The Knowledge Discovery Cube Framework
A Reference Framework for collaborative, information-driven pharmacovigilance

by

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Submitted for the Degree of Doctor of Philosophy

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Declaration

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Abstract

Pharmacovigilance has attracted enormous attention over recent decades. At present, the increasing datafication combined with the growing knowledge elicitation capabilities of key technology innovations, present pharmacovigilance with enormous opportunities to improve its effectiveness and widen its scope. With change being a continuous process, for pharmacovigilance this represents an era of “Digital Darwinism”, during which new directions are opening fast and new challenges emerge, as to how the sector adapts in order to draw benefit. Current efforts and initiatives, aimed at addressing existing barriers and at enhancing the practical applications of new science and technology, are fragmented and disjoint, and thus are not adequate to provide an effective response to challenges. This research proposes a new paradigm for collaborative, information-driven innovation in pharmacovigilance and develops a Reference Framework, in order to (a) deepen the collective understanding of how a principled, collaborative and balanced medicines safety data ecosystem can be organised, (b) guide stakeholders towards the optimisation of pharmacovigilance and (c) provide useful reference points for the ongoing research and development process in the field. The Knowledge Discovery Cube (KDC) Framework provides the means for continual analysis, and for managing technology adoption in an informed and intentional manner. A variety of sources informed the research work. The resulting deliberations draw on the findings and conclusions of scholarly research, guidelines, policy documents and reports, and other resources from within and outside the field of health and life sciences, as well as on relevant theories. The developed framework was operationalised and validated in the context of vaccine safety monitoring.
Acknowledgement

Firstly, I would like to express my sincere gratitude to my supervisor Prof. Lampros Stergioulas for the continuous support of my Ph.D study and related research, for his patience, motivation, and immense knowledge. His guidance helped me in all the time of research and writing of this Thesis.

I would like to thank the rest of my thesis committee: Prof. Jyoti Choudrie and Dr. Rosanna Cole, for their insightful comments and encouragement.

My sincere appreciation goes to the partners of the ADVANCE project. Without they precious support it would not be possible to conduct this research.

I gratefully acknowledge my dear friends for their assistance and encouragement.

Lastly, but most importantly, I wish to thank my family for their endless support and encouragement.
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<td>Adverse Drug Reaction</td>
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<tr>
<td>ADE</td>
<td>Adverse Drug Event</td>
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<tr>
<td>ADVANCE</td>
<td>Accelerated Development of VAccine beNefit-risk Collaboration in Europe</td>
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<tr>
<td>B/R</td>
<td>Benefir-Risk</td>
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<td>BRA</td>
<td>Benefit-Risk Assessment</td>
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<td>CT</td>
<td>Clinical Trial</td>
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<tr>
<td>EBPs</td>
<td>Evidence-Based Practices</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
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<tr>
<td>ENCePP</td>
<td>European Network of Centres for Pharmacoepidemiology and Pharmacovigilance</td>
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<td>EPC</td>
<td>Event-driven Process Chain</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>ICH</td>
<td>International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use</td>
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<td>ICT</td>
<td>Information and Communication Technologies</td>
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<tr>
<td>IoT</td>
<td>Internet of Things</td>
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<td>IMI</td>
<td>Innovative Medicines Initiative</td>
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<td>KDC</td>
<td>Knowledge Discovery Cube</td>
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<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<td>POC</td>
<td>Proof Of Concept</td>
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<td>RCT</td>
<td>Randomised Clinical Trial</td>
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<td>RI</td>
<td>Research Investigation</td>
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<td>RQ</td>
<td>Research Question</td>
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<td>SRS</td>
<td>Spontaneous Reporting System</td>
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<td>WHO</td>
<td>World Health Organisation</td>
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<td>Work Package</td>
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Chapter 1: Introduction

“Research is to see what everybody else has seen and to think what nobody else has thought”

Albert Szent-Györgyi, Hungarian scientist, Nobel Prize in Physiology/Medicine (1937)

1. Introduction: Origins and scope of pharmacovigilance

Issues related to drug safety have attracted enormous attention over recent decades (Laporte, 2016). Pharmaceutical products are used in or on the human body for the prevention, diagnosis or treatment of disease, or for the modification of physiological function (WHO, 2002a; 2002b). Modern drugs have changed the way in which diseases are managed and controlled. However, adverse reactions to medicines are a common cause of illness, disability or death, even though they are often preventable (WHO, 2002b, 2004; Lazarou et al., 1998). Studies have shown that adverse drug reactions (ADRs) are probably responsible for millions of deaths globally each year (in 2008, 197,000 ADR-related deaths were reported in the EU alone, according to official EC statistics), in both in- and outpatient settings (Bouvy et al., 2015). 6.5% of UK hospital admissions are due to ADRs, and almost 15% of UK patients experience an ADR during their admission (Davies et al., 2010). In France, the estimated annual number of ADR-related hospitalisations was 144,000 in 2007 (BnardLaribire et al., 2015). A recent study in Spain estimated that the incidence of ADR-related hospitalisations was 7.11%, with fatal ADRs amounting to 1.97% (Esteban et al., 2017). ADR occurrence in an outpatient setting cannot be fully estimated, as currently such studies are scarce (Lazarou et al., 1998). The overall impact of ADRs is high, accounting for considerable morbidity, mortality, prolonged hospital stays and extra costs. Although many of the implicated drugs have proved benefit, measures need to be put into place to reduce the burden of ADRs and thereby further improve the benefit-risk ratio of the drugs (Pirmohamed et al., 2004). Enhancing the post-market surveillance of health and medicine products is of paramount importance for public health and of high priority for all pharmaceutical stakeholders (industry and regulators), particularly since many adverse events are not captured in randomised clinical trials (RCT), and previously undetected adverse reactions may occur as the
drug is exposed to patients and situations not controlled for during the clinical trial. The effective monitoring of medicines safety is of particular importance in fields characterised by an extensive and prolonged use of pharmacological treatment, e.g. the field of psychiatry (Spina & Trifirò, 2015). The practice of monitoring the safety of medicines is commonly referred to as **pharmacovigilance**. Pharmacovigilance is defined by the World Health Organisation (2002) as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term side effect, of medicines”. The practice of pharmacovigilance is sometimes called postmarket (or post-market) surveillance or post-authorisation monitoring. Within the scope of pharmacovigilance fall the detection, assessment, understanding and prevention of adverse effects or any other possible medication-related problems of herbals, traditional and complementary medicines, blood products, biologicals, medical devices and vaccines. The term **adverse drug reaction** (ADR) is used to refer to “a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function” (WHO, 2002a).

The origins of pharmacovigilance can be traced back to the case of thalidomide (Waller, 2011; Caron et al., 2016). Thalidomide was first marketed in Germany in October 1957, used as a sedative for the treatment of morning sickness during the early stages of pregnancy. In 1959 the first cases of babies born with phocomelia, a congenital malformation of the limbs, were reported in Germany. The number of cases of phocomelia associated with thalidomide intake grew to an estimated 10,000 cases globally, but a causal association with the medicine was refuted by the manufacturer. In 1961 a link was discovered between pregnant mothers receiving the drug Thalidomide and then giving birth to infants with congenital malformations (McBride, 1961). Thalidomide was subsequently withdrawn from the market in the majority of countries. Pharmacovigilance under the spotlight in the aftermath of the thalidomide incident. Prior to the thalidomide disaster, in most countries there were no formal drug regulation systems in place to monitor the safety of medicines. The thalidomide case highlighted the importance of drug safety and prompted the start of systematic approaches to monitor the safety of marketed medications (WHO, 2002a). Since the 1950s, several medicinal products have been withdrawn from market, as a result of evidence of unknown adverse reactions (Fung et al., 2001; Olivier & Montastruc, 2006; Onakpoya et al., 2016). According to the WHO (2004), effective pharmacovigilance
systems can help improve both patient, and overall public, health and safety in relation to the use of medicines. Pharmacovigilance can provide valuable insights regarding the benefit, harm, effectiveness and risk of medicines, to support their safe, rational and more effective (including cost-effective) use. The timely signalling of adverse drug effects is required, in order to promote the safety and quality of drug therapies. Pal et al. (2013) note that public health programmes need to quantify and characterise risks to individuals and communities from their medicines, to minimise harm and improve use, to sustain public confidence in the programmes, and to track problems due to medication errors and poor quality medicines. The WHO (2000) summarises the major tasks of pharmacovigilance as follows:

- Early detection of unknown adverse reactions and interactions.
- Detection of increases in frequency of known adverse reactions.
- Identification of risk factors and possible mechanisms.
- Estimation of quantitative aspects of benefit/risk analysis and dissemination of information needed to improve medicine prescribing and regulation.

Traditionally, post-market safety surveillance has relied on data from spontaneous reports of adverse events, medical literature, and observational databases, coupled with other pharmacoepidemiological and clinical research studies (McNaughton et al., 2014). Limitations of these data sources include potential under-reporting, lack of geographic diversity, possibility of patients’ perspectives being filtered through healthcare professionals and regulatory agencies, and time difference between event occurrence and discovery (Powell et al., 2016; Salathé, 2016). The need to enhance patient safety calls for a proactive approach to pharmacovigilance, in order to improve patient care and safety in relation to the use of medicines (WHO, 2002a).

Currently, the rapidly increasing supply of information, combined with advances in technological capabilities for knowledge elicitation, present pharmacovigilance, and the related fields of epidemiology and pharmacoepidemiology, with enormous opportunities (Yeleswarapu, et al., 2014; Bellazzi, 2014; Harpaz et al., 2016). Today's biggest trend is data. New data is created in novel ways, and processed and analysed with the help of new and increasingly intelligent methods. Health-related information is increasingly shared online by patients, emerging as a potentially valuable, yet largely unexploited at present, source of post-market safety data that could supplement data from traditional sources of drug safety information. In this context, safety monitoring is expanding its evidence base, moving beyond traditional approaches.
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towards sophisticated methods that can identify possible safety signals from multiple, primary and secondary, information sources, both structured and unstructured. Secondary data sources include electronic health records (EHR), social media data, etc (Harpaz et al., 2016; Ehrenstein et al., 2017). New proactive forms of safety monitoring are emerging, featuring real-time monitoring and rapid learning systems (EMA 2015).

Important aspects of current practices and emerging trends in pharmacovigilance are investigated in Chapter 2.

2. The research problem: Rationale and motivation

The safety monitoring of drugs already on the market represents an increasing concern for the sector. There is a growing interest in innovative methods for real world evidence generation from real world data in relation to medicinal products (CIOMS,2013; Beninger, 2016; STAMP Commission, 2016; Salathé, 2016; Tuccori & Wallberg, 2017). The proliferation of secondary data sources coupled with advances in signal detection technologies can bring significant advantages, reduce the monitoring and reporting cycles for adverse events and generate new insights to improve drug safety (Edwards & Bencheikh, 2016; Furlan et al., 2016; Meyboom et al., 2017; Carvajal et al., 2017). This includes data from traditional sources such as electronic medical records (EMRs) and from non-traditional sources such as social media. Finding ways to include new sources of safety information poses new challenges to safety monitoring. Technology is regarded as a main driving force in shaping the future of pharmacovigilance. Rapidly developing innovations in biomedical informatics have made significant contributions to the infrastructural development of pharmacovigilance (Beninger & Ibara, 2016).

The future is not predetermined, but can evolve fast and in different directions: technology evolution processes are usually nonlinear and unpredictable (Kostoff & Schaller, 2001). For businesses today represents an era of “Digital Darwinism,” (Schwartz, 1999; Solis, 2011; Kreutzer & Land, 2014): technology and society are evolving faster than businesses can naturally adapt, and threatening their competitiveness and long-term survival. Similarly, at present, both pharmacovigilance regulators and industry are under increased pressure to evolve. Pharmacovigilance undergoes its own era of “Digital Darwinism”, with digital innovation holding the key to transformation. It is a time when society and technology evolve fast, introducing new directions and challenging how the sector adapts in order to draw benefit.
Pharmacovigilance is experiencing a paradigm shift, and is faced with challenges that can broadly be described in two dimensions: on the one hand pharmacovigilance systems are extending their scope from a systematic and health organisation-driven perspective towards the inclusion of “real-world” evidence and the “consumer” input, while at the same time the technological and methodological means employed are evolving from established sector-specific approaches towards the take-up of technical innovations from other sectors.

The goal of pharmacovigilance is not to simply generate more signals, but to generate better signals and to apply the finite resources available to identifying safety issues and implementing programs to help mitigate them. The scope of pharmacovigilance is widening beyond signal detection towards deciphering other aspects of drug safety information that can help improve the management and treatment of ADRs and directly serve the health of the public. For example, harnessing information that characterises the use of medicines in everyday practice and people’s attitude and behaviour towards ADRs, can be of use to healthcare professionals for optimising treatment (Pitts et al., 2016; Böhm et al., 2016; van Puijenbroek & Harmark, 2017).

The increased supply of information, combined with the growing knowledge elicitation capabilities of key emerging technologies, present pharmacovigilance with enormous opportunities. Currently, safety monitoring is expanding its evidence base, moving beyond traditional approaches (i.e. monitoring and statistical analysis of databases of spontaneously reported suspected adverse reactions) towards sophisticated methods that can identify possible safety signals from multiple information sources, both structured and unstructured. The way forward is the development of knowledge exchange infrastructures that integrate various types of medical data and information (e.g. medicines information, medical data, demographical data, epidemiological data, biomedical data, clinical trial results, etc.) to improve work patterns, processes, and efficiencies across the safety monitoring value chain.

As technology advances, the capabilities of investigation methods evolve and while they move towards a maturity level, there is always a trade-off between the potential benefits and the limitations associated with their use, which needs to be considered in the design of real-life vigilance systems. This is the reason why formal pharmacovigilance schemes appear hesitant or slow in the adoption of cutting-edge innovations, although they acknowledge that technology can help explore different types of medical information to uncover the traces of new knowledge not
readily apparent in formal approaches. Several key uncertainties emerge when examining the current state:

- Are we getting the most value out of the available knowledge sources?
- Are we getting the most value out of the available technologies?
- Can we support emerging needs?
- How could we make the most of existing data?
- How could we best utilise data from new sources?
- Can stakeholders adopt new technologies and innovations?

The answer to these questions is not straightforward and a distinction needs to be made between the actual value achieved in real-world situations and the theoretical capabilities of technologies and innovations. This is because, although technology and scientific innovations form an essential part of the investigation environment, in real-world situations usable knowledge can only be generated when innovation meets certain preconditions regarding the: data life-cycle, organisational conditions, work-effort needed, timeliness for results, barriers for approval and code of conduct to be followed, etc.

A look at research in the field during the past decade reveals a series of euphoric scholarly announcements about research studies and new information technology innovations that have managed to successfully identify signals of adverse drug events from new potential sources (e.g. social media data). In practice, however, pharmacovigilance systems still struggle to incorporate such solutions into their work processes. The core of regulated pharmacovigilance practice still revolves mainly around spontaneous reporting, featuring the collection of individual case safety reports, their quantitative analysis and subsequent clinical assessment (Santoro et al., 2017). Despite considerable research activity towards leveraging new data sources, the process is still filled with barriers and challenges. As a result, a comparison between the hype of the research world and the reality of day-to-day pharmacovigilance praxis for pharmaceutical companies and regulators reveals that foreseen benefits have not fully materialised. This clearly highlights a strong need for further investigation, which triggered the motivation for the present research work, namely, to develop a Reference Framework to bridge the gap between research and practice and provide a solution for the problem faced by medicines regulators and industry.
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Scientific research in itself is not sufficient. Other foundational capabilities must also be in place. Operationalisation, and thinking “in context” are imperative in order to be able to extract value out of emerging innovations. In the case of medicines, the process of moving to praxis innovations regarding the development, assessment and lifecycle management of medicinal products entails a strong regulatory dimension, which often remains underappreciated (Hamburg, 2011). Given the complexity of the endeavour, the regulatory embedding of medicines innovations is evolving into a scientific discipline of its own. Regulatory science is aimed at the optimisation of scientific and technological developments according to objectives geared toward human health (Kirino, 2015). Regulatory science is described as the science of developing new tools, standards, models, and approaches to assessing the efficacy, safety, manufacturing quality, and performance of medical products and facilitate a sound and transparent regulatory decision making throughout medicines development and life cycle management (Moghissi et al., 2014; Spindler et al., 2016; Kurz, 2017). Therefore, regulatory science is concerned with a large variety of activities and outputs, from new techniques and products to methodological standards and guidance, as a means to improve regulatory practice (Kurz, 2017). Kirino (2015) emphasises that harmonising technology with society’s needs can be accomplished only “by accurately comprehending and carefully exploiting the characteristics and trends of new technologies, reactions, materials, and substances”.

Internationally, several initiatives have been launched, aimed at addressing challenges in drug development and regulation, e.g. FDA’s “Advancing Regulatory Science Initiative” in the USA (FDA, 2011), The Innovative Medicines Initiative (IMI) in Europe (Goldman et al., 2014), etc. Within their research agenda, particular emphasis is placed on increasing the utility of real-world evidence to support regulatory decision-making on medicines. Research initiatives are focusing on different aspects of the topic: on real-world data sources, methodologies, analysis model, infrastructure (platforms), and governance model (Kristensen et al., 2009; Anes et al., 2012). Their outputs typically include new techniques and products, new methodological standards and guidance. On an EU level, examples include, initiatives aimed at promoting:

<table>
<thead>
<tr>
<th>Scope</th>
<th>Initiatives</th>
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<tbody>
<tr>
<td>patient registries</td>
<td>PARENT Joint Action, ENCR-European Network of Cancer Registries, Eurocourse and the EMA Initiative on Patient Registries</td>
</tr>
<tr>
<td>electronic health</td>
<td>EH4CR, EMIF, EU-ADR Alliance, RD-Connect, epSOS, EuroRec</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Scope</th>
<th>Initiatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>records data valorisation</td>
<td>IMI GetREAL, IMI PROTECT, IMI ADAPT SMART, IMI ADVANCE, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance- ENCePP</td>
</tr>
<tr>
<td>health technology assessment (HTA)</td>
<td>EUnetHTA network for HTA across Europe (support permanent collaboration on post-launch evidence generation)</td>
</tr>
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Similarly, international regulatory organisations are expanding their guidance in the direction of incorporating real-world evidence (EMA, 2013; WHO, 2002a, 2002b, 2004, 2006; FDA, 2005a, 2005b) and scholars are already calling for systems-based approaches (Furlan et al., 2016). Cross-continuum data analysis is not just about the work of individual stakeholders or about the development of data hubs. Innovation derives from harnessing the power of interconnected capabilities, thinking and effort. However, changing the activity from a traditional approach to one based on knowledge organisation makes it imperative to elaborate new methodologies that build on dynamic synergies. The medicines safety innovation landscape is already showing signs of a gradual evolution into an ecosystem, shifting its methods, processes, cultural habits and competencies from episodic management of drug safety challenges to more holistic, continuum-oriented approaches. Working in this direction, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) was established, under the coordination of the European Medicines Agency (EMA). ENCePP brings together public institutions and research organisations involved in pharmacoepidemiology and pharmacovigilance research.

However, despite progress, existing standards, methodologies, and guidelines aimed at helping pharmacovigilance stakeholders improve their operations; offer a narrow perspective on pharmacovigilance, failing to take a systemic approach. Technology is advancing at a rapid pace; nonetheless, the benefits for pharmacovigilance are limited, as the adoption of innovations for medicines safety monitoring remains rather slow.

The main challenge identified by the present work is that **current efforts and initiatives, aimed at addressing existing barriers and at enhancing the practical applications of new science and technology, are fragmented and disjoint, and thus are not adequate to provide an effective response to the challenges identified above.**
3. The present inquiry

Objective of the present research work is to develop a comprehensive Reference Framework, highlighting critical dimensions of the investigation and defining components necessary to support the migration to and subsequent upkeep of information-driven drug safety investigations.

3.1 Why do we need a framework?

Medicines safety investigations are not just about interlinking repositories or about inter-computer networking. For a given medicines safety investigation, a holistic approach is needed in order to recognise data flows, workflows and business processes to then be able to develop appropriate policies and measures. Technology needs to be positioned in relationship to the tasks to be carried out, the people involved and the organisational structure. Overlooking a set of indicators or failing to balance requirements may jeopardise the success of the study.

The complex nature of the emerging medicines safety landscape and the need to confront new and complex Research Questions (RQ), exploring and combining diverse knowledge sources, a general framework is needed to guide the implementation of the evidence creation process and the development and implementation of new technologies and methods for insight generation. There cannot be a “one size fits all” methodology, and so best practice in method development for drug safety investigations calls for the incorporation of a framework of artefacts, tools and techniques that can be tailored to the nuances of each investigation scenario, and the situational context and capacities of the organisations that want to implement it. The Reference Framework is built to remedy that problem by highlighting aspects of methodology such as process, techniques and artefacts needed to embrace information-driven pharmacovigilance in a structured manner. Ultimate objective of this effort is the semi-automation of this process. We argue that effective drug safety investigation systems need to take into account both technical and social aspects. In order to draw an accurate picture of the situation to be addressed and define a suitable solution, technological options need to be examined in context.

There are different pathways linking what starts as a RQ (theoretical/ scientific protocol), and its underlying causal assumptions, to the outcomes produced. In order to achieve this, it is necessary to understand:
• the implementation, both in terms of how the RQ is implemented and the quality of what is delivered;
• the mechanisms of impact linking RQ implementation activities to outcomes;
• how the context in which the RQ is investigated (e.g. external factors) affects both what is implemented and how outcomes are achieved.

Focus should be placed on the needs of the research question investigation lifecycle, and its contextualisation in the actual implementation environment and on alignment with the perspectives of the involved stakeholders. By leveraging existing capabilities, the diverse needs of individual stakeholder groups should be met, also ensuring effectiveness and scientific value of the investigation.

An essential element of defining and implementing best practices in the area of patient safety and regulatory compliance strategy is the fine interplay between domain knowledge, streamlined processes and technology innovation. When designing a drug safety investigation, a comprehensive view over several aspects is required, so as to understand their interdependencies and implications. While extensive guidance exists with respect to the scientific and regulatory dimension of investigations (i.e. “what” should be), less attention is given to their systematisation (i.e. “how” this can be achieved). The latter can be a complicated task. Investigations bring together a set of interacting elements to serve a collective purpose. Their interrelationships span several layers (data and information, technical, organisational), making their development a complex process. Once an investigation becomes an established practice, the need of maintenance/optimisation in also present. Maintenance/optimisation can be described as a sequence of (re)development processes, which, however, take place against a different set of contextual factors, as the environment itself is evolving at the same time. Because the contextual factors that condition the investigation change, the decisions and assumptions made during the original design or earlier re-development phases need to be revisited. The ability to handle uncertainty (in the form of new developments) can be the critical limiting factor for drug safety investigation systems. Galbraith (1974) believes that "the greater the uncertainty of the task, the greater the amount of information that must be processed between decision makers during the execution of the task to get a given level of performance".

This calls for a structured approach for managing the lifecycle of an investigation implementation (development and maintenance/optimisation of the investigation system).
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Presently, there exists no general comprehensive reference framework to guide the investigation, implementation and sustainment of collaborative information-driven medicines safety innovation processes. Related work has focused on developing guidance for protocol development, implementation aspects, or reporting outcomes, but no comprehensive reference framework has been proposed to accommodate the complete life-cycle, with a view to incorporate technology and other innovations and changes and the emerging paradigms of pharmacovigilance. While useful insights can be drawn from these works, their limitations are significant, since proposing a comprehensive general reference framework for the area of medicines safety investigations was not their intended purpose. It should be acknowledged that important insight can also be found in areas beyond pharmacovigilance.

Aim of the present inquiry is to develop a framework that is informed, in terms of its relationship to the application domain and pragmatic, with the ability to adapt and enable action as knowledge and technologies evolve. While ad hoc initiatives focus on short-term or narrow-range objectives, the use of the Reference Framework should enable long-term and broad-scope value-creating activities.

3.2 What is the purpose of a Reference Framework?

Banathy (1996) describes system design as a “decision-oriented disciplined inquiry”. Hatley and Pirbhai (2013) note that systems and the process of developing them are levelled hierarchies, while Sheu (1997) stresses that the design process involves decomposition of artefacts and their relationships and refinement in the form of specification. A Reference Framework represents a key instrument in the conceptualisation and development process, allowing to set strategic directions, to ask “the right questions” about critical aspects and guide users’ thinking and understanding.

According to OASIS (Organisation for the Advancement of Structured Information Standards) a reference model is "an abstract framework for understanding significant relationships among the entities of some environment, and for the development of consistent standards or specifications supporting that environment". Although a framework is a structured method of going about systems, it is not prescriptive of their implementation. A reference framework is not directly associated with any standards, technologies or other concrete implementation details. Its purpose is to provide a common semantics that can be used unambiguously across and between different
implementations. The benefit of this approach is that it allows to ascertain the key constraints and characteristics of the investigation process. Elements of the framework can be mapped to each other in different ways to support alternative implementations for a variety of research questions and shed light to the process from the viewpoint of individual stakeholders. In any given domain, a Reference Framework (RF) provides a common backplane for consistency, collaboration, sharing, and reuse.

The first step for developing a Reference Framework is to establish its objectives, scope and intended audience. An understanding of the objectives for establishing a Reference Framework is critical for determining the framework development activity, its processes and components. The principal applications of a reference framework for medicines safety investigations are to (a) support the definition of the research question(s) underpinning the investigation and the organisation of the design and implementation of the investigation; (b) ensure the scientific coherence and the operational effectiveness of the investigation; (c) facilitate the optimisation of the investigation and (d) promote innovation.

The scope of a Reference Framework is determined by the extent of the domain which it covers, and its organisational reach or applicability, which in the present case refers to medicines safety investigations in the context of pharmacovigilance. In the case of medicines safety investigations, a reference framework can help establish operational coherence, drawing together and consolidating the multiple perspectives that underpin the complex pharmacovigilance ecosystem within which safety-related knowledge is produced. The reference framework can provide: (a) a common language among all involved stakeholders; (b) epistemological and methodological grounding within appropriate theories and guidelines; (c) guiding points against which pragmatic decisions can be made; (d) practical directions to the design and development of investigations; (e) a structure for the organisation of collaborations; and (f) a structured approach to managing required capacities in order to deliver on objectives.

On the basis of the Reference Framework, several aspects pertaining to the lifecycle of an investigation can be planned, managed and controlled in a systematic way. This includes the following: outputs produced, assets employed, process organisation, governance policies, and roles and responsibilities of participating individuals and organisations. The use of an effective Reference Framework enhances understanding, improves productivity and consistency and facilitates governance. On the contrary, the absence of a comprehensive reference framework can
reduce stakeholders’ understanding of the process and of the situational factors affecting it. It can undermine their capacity to ascertain the key constraints and characteristics of the investigation and of the implementation context and potentially inhibit the ability to effectively implement and optimise the process.

The development of a Reference Framework is also aimed at putting existing guidance in context. The Framework relies on and does not overlook existing guidelines, recommendations and standards. It represents a fundamental starting point to guide deliberation and action based on relevant guidance. In order to be effective, the provisions of a Reference Framework for pharmacovigilance investigations need to be: (a) Clear (easily understood and practiced); (b) Useful (reflecting important dimensions of the investigation); (c) Reliable (allowing for consistent review of different aspects of the investigation implementation); (d) Valid (providing a true indication of what is important); and (e) Practical (timely applicable, at reasonable cost and effort, and flexible enough to inform and influence decisions to accommodate progress and innovation). Components of a Reference Framework include the concept model, reference architecture, process and organisation view. Together they describe the lifecycle of collaborative information-driven drug safety investigations.[d1] The Concept Model explains the core concepts of this lifecycle and their inter-relationships. The Reference Architecture provides an overview of the process at different levels of abstraction. The Reference Process presents the sequencing of activities, while Organisation defines the roles and responsibilities of the participants. Building on the definitions of March & Smith (1995) the main components of the Reference Framework are (a) its Constructs (concepts), representing the vocabulary of the domain, a “conceptualisation used to describe problems within the domain and to specify their interrelationships; and (b) model, i.e. a set of propositions or statements expressing relationships among constructs.

3.3 Can we use an existing Reference Framework?

The effective transfer of knowledge from theory to practice is a primary concern in various disciplines. In research literature, the gap between theory and practice has been framed as a knowledge transfer problem, as concerning two distinct kinds of knowledge, and as a knowledge production problem (Van de Ven & Johnson, 2006). The present inquiry could be viewed as research into translation, described by Davidson (2011) as research into the methods of
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**translation**, namely, research that is aimed at discovering how to best progress along the translational pathway from science to the achievement of practical outcomes and vice versa. Purpose of the inquiry is to investigate and address particular gaps in the methods of translating research into practice: from research into new pharmacovigilance methods to the uptake of and practical implementation of these innovations, the development of policy etc., for the effective post-marketing safety surveillance of medicines.

**Knowledge Translation** is a prominent topic in **healthcare**, as scholars in the field acknowledge that evidence from clinical research is necessary but not sufficient for the provision of optimal care (Glasgow et al., 1999; Straus et al., 2009; Straus et al., 2013; Harvey & Kitson, 2015). Early implementation science studies considered the lack of a comprehensive, multi-perspective evaluation framework as the reason hampering progress in public health interventions (Glasgow et al., 1999). Later, the need for a more holistic perspective was recognised. Knowledge Translation, which is sometimes called Research Translation or Knowledge Transfer (although knowledge transfer implies a linear process), is concerned with both the implementation of research evidence and the evaluation of its impact for the purposes of ensuring findings from academic research are practical and of implementing evidence-based solutions. Knowledge Translation is about closing the gaps from knowledge to practice, namely, between evidence and decision-making (Straus et al., 2009), and about the acceleration of the knowledge cycle of transformation of knowledge into use (Schryer-Roy, 2005). The practical use of research knowledge (**research utilisation**) can be linear (knowledge-driven or problem-solving model, depending on whether the process is driven by theory or by praxis) or co-created (interactive model) (Weiss, 1979).

Knowledge Translation is a widely used and studied concept in healthcare, being regarded as an “ethical urgency”, since it concerns improving the quality of care and decreasing the risk of adverse events, and as a managerial priority, since it can help optimise the return on investment in research (Straus et al., 2013). Unlike pharmacovigilance, in healthcare several holistic frameworks have been proposed for the purposes of enhancing Knowledge Translation in the field (Graham et al., 2006; Straus et al., 2013; Khoddam et al., 2014). Their aim is to provide guidance to allow practitioners to define and describe Knowledge Translation, and outline strategies to enhance the Knowledge Translation capacity of all involved stakeholders, and
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facilitate the implementation of Knowledge Translation activities, by integrating the roles of knowledge creation and knowledge application (Graham et al., 2006; Straus et al., 2013).

Nonetheless, in health and medical literature there is little consensus about what Knowledge Translation is, and about its defining attributes (khoddam et al., 2014), with different scholars focusing on specific aspects of translation and application contexts. khoddam et al. (2014) summarise the defining attributes of Knowledge Translation as follows:

<table>
<thead>
<tr>
<th>Element</th>
<th>defining attribute</th>
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<tbody>
<tr>
<td>knowledge</td>
<td>Use of refined knowledge, consistent with context characteristics and user needs</td>
</tr>
<tr>
<td>activities</td>
<td>Application of dynamic, comprehensive, evaluation-based, user-oriented, context-based and on-time activities</td>
</tr>
<tr>
<td>context</td>
<td>Occurrence in a multidisciplinary, social, interactive, collaborative and dialogue-based context</td>
</tr>
<tr>
<td>output</td>
<td>Production of cost effective, timely and clinically effective outputs.</td>
</tr>
</tbody>
</table>

Important antecedents of the Knowledge Translation process, fall under the following categories: an integrated source of knowledge, a receptive context, and preparedness (khoddam et al., 2014). The success of the process is significantly conditioned by the occurrence of these conditions. The present research sets out to develop a Reference Framework to deepen the collective understanding of how a principled, collaborative and balanced medicines safety data ecosystem can be organised and to provide useful reference points for the on-going research and instantiation process in the field. Recognising the multidimensional and complex nature of pharmacovigilance, and the current lack of a holistic overview, the present research cannot use a partially relevant Knowledge Translation framework as its starting point, since the meaning of Research Translation in the field of pharmacovigilance needs first to be determined. For this reason, the present inquiry opts for an inductive approach that is grounded in data, informed by theory and validated in practice.

3.4 Conceptualisation of the KDC Reference Framework

The preliminary study of the pharmacovigilance domain has demonstrated that there exists no Reference Framework for collaborative, information-driven pharmacovigilance innovation, despite the fact that current needs and emerging visions for the future of pharmacovigilance clearly point in this direction.
The present research builds on the following argument: while the investigation process is inherently knowledge intensive, relying upon the identification and application of rigorous, state-of-the-art scientific methods and technologies for evidence elicitation, value can be achieved only if relevance to the actual application context is ensured. Technological innovations contain interdependencies between technology, people, the socio-cultural environment, structure and organisation of the application domain. Operational accommodation of innovation can only be achieved through a holistic examination of all dimensions, recognising the significance and improvement capacity of technologies, as well as their limitations in view of environmental constraints. An in-depth investigation of the socio-technical ramifications of knowledge discovery is imperative in order to develop effective work processes for knowledge extraction in real-life situations. This is particularly the case in regulation-bound domains, like pharmacovigilance. In a given socio-technical context, safety monitoring mechanisms make use of the available information sources and relevant socio-technical capabilities to achieve value.

According to the preliminary investigation of relevant scholarly outcomes and empirical findings, the analysis dimensions to be considered during the design of a Smart Investigation Environment for a given RQ comprise: the scope of the investigation, the information sources available, the existing socio-technical capabilities and their limitations, so as to assess the value proposition of this implementation. The resulting evidence creation processes are workflows combining technologies with human-lead processes. Leveraging real-world evidence and new technologies calls for pharmacovigilance to develop smart custom-made investigation environments for the early detection and assessment of signals of adverse reactions on the basis of holistic approaches for intelligent information processing and integration. The present research work adopts a holistic view on information and technology innovation in the area of pharmacovigilance. The overall objective, as updated, is to:

(a) investigate and set the foundations for a holistic Reference Framework for knowledge management in pharmacovigilance (Knowledge Discovery Cube Framework), in order to

(b) promote the development of Smart Investigation Environments (SIE) on the basis of intelligent information processing and integration and

(c) validate this approach in the context of vaccine benefit-risk analysis.
Smart Investigation Environments are envisaged as digital knowledge discovery “laboratories” for evidence elicitation, resulting from the instantiation of the Reference Framework. Their aim is to provide the best evidence at the right time to support decision-making regarding the safety of licensed medicinal products. For the purposes of the investigation of a given Research Question (RQ, i.e. an investigation hypothesis based on a research/scientific protocol), situated in a certain socio-technical context, attainable and relevant information items are brought together and analysed to produce knowledge. The design process spans the Information sources and Technology space (rigor perspective) and the Organisational and Regulatory space (relevance perspective), examining them as a continuum. Overall, the design process strives to: achieve scientific validity of results and innovation, to ensure optimal process performance, and to make optimal use of technology tools and infrastructures, while at the same time conforming to the existing regulatory framework and meeting relevant quality standards, complying with process governance, inter-organisational exchange and allowing for stakeholder satisfaction. Aim of this research is to establish and validate a Reference Framework for drug safety investigations suitable for an evolving technological and social landscape. The principle function of the KDC Reference Framework is to align and coordinate the broad set of capabilities needed for setting up drug safety investigations and studies that meet particular outcomes. This goes beyond the establishment of technical capability and competence and involves a strong social dimension.

The proposed framework for the design of a Smart Investigation Environment for the investigation of any safety monitoring question is titled “Knowledge Discovery Cube Framework”. The purpose of developing a Reference Framework is to deepen the collective understanding of how a principled, collaborative and balanced medicines safety data ecosystem can be organised and to provide useful reference points for the ongoing research and innovation instantiation process in the field. A reference framework is more than a mere checklist, an assessment methodology or an implementation framework. The Organisation for the Advancement of Structured Information Standards (OASIS, 2006) describes a reference model as an “abstract framework for understanding significant relationships among the entities of some environment, and for the development of consistent standards or specifications supporting that environment”. The aim of the present inquiry is to develop a Reference Framework that is informed (in terms of its relationship to the application domain, and
knowledge) and **pragmatic** (in terms of its ability to enable learning and action as circumstances change and knowledge evolves). This will allow practitioners to establish baseline references to help define, design and implement electronic investigation/research protocols, effectively exploring diverse knowledge sources in a given implementation context.

### 3.5 Research purpose

Advanced digitisation is transforming science and society, and reshaping the field of pharmacovigilance. The purpose of the present research is to explore the emerging landscape in pharmacovigilance and to develop a **Reference Framework for collaborative, information-driven innovation in the field of pharmacovigilance** that can be used to describe and assess the implementation of medicines safety investigations, as well as to guide and educate stakeholders towards the design, optimisation and innovation of pharmacovigilance implementations.

Against the backdrop of the Medical/Drug data and technology revolution, the Knowledge Discovery Cube Framework represents a **method for continual analysis**, a mechanism for managing technology adoption in an informed and intentional manner. At any given instance, the Knowledge Discovery Cube Framework will help assess the existing conditions to identify the capabilities and risks of the process (Capability determination) to derive considerations and recommendations and develop opportunities for future improvement. In that sense, the Framework will support the implementation of any Evidence Creation Process: it will provide insight and reveal areas of potential improvement to be considered for the setup of the Evidence Creation Process.

Typically, research studies are classified according to their research purpose as: exploratory, descriptive or explanatory (Saunders et al., 2009). A research project may have more than one purpose. In principle, the present research is of an exploratory nature, as it entails a search for new insights in the evolving domain of pharmacovigilance, in an effort to develop new, and relevant ways of looking at things, and to lay the foundations that will lead to future studies and eventually to the implementation of new pharmacovigilance methods. An exploratory research design is deemed most useful for inquiry projects that are addressing a subject about which high levels of uncertainty exist. In this light, the present study sets out to develop a new and comprehensive understanding of the topic, starting with a broad focus initially, which becomes progressively narrower as the inquiry advances. The inquiry proceeds in an explanatory
direction, aiming to define and explain the relationships between the identified variables. This is pursued mainly by means of qualitative data collection and analysis.

3.6 Research objectives

Research objectives describe what one aims to achieve by a research project. In order to accomplish the research purpose of the present research, the following detailed objectives are set, which fall into three distinct areas:

I. Exploration of the pharmacovigilance domain
   1. Develop an in-depth understanding of pharmacovigilance investigations and the emerging evidence landscape and define concepts and paradigms relevant to this study. (O₁)

II. Development of Reference Framework
   2. Explore relevant models and theories in the field and beyond, and identify concepts and paradigms relevant to this study. (O₂)
   3. Define design requirements for a Reference Framework. (O₃)
   4. Develop the KDK Reference Framework on the basis of the identified requirements and learnings from relevant models and theories. (O₄)

III. Empirical validation
   5. Verify that the Reference Framework satisfies all the design requirements. (O₅)
   6. Operationalise and validate the Reference Framework in practice. (O₆)

Research work undertaken towards the achievement of the aforementioned objectives is detailed in the following Chapters. This dissertation is organised into six chapters. With regards to the research objectives, the Exploration of the pharmacovigilance domain (I) is detailed in Chapter 2. The Development of a Reference Framework for pharmacovigilance innovation (II) is discussed in Chapter 4. The operationalisation and empirical validation of the developed framework (Knowledge Discovery Cube, KDC Framework) (III) is presented in Chapter 5.
4. Outline of the Dissertation

The dissertation is organised in six Chapters, as follows:

Table 3. Outline of the Dissertation

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Scope</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Introduction</td>
<td>Scope and objectives of the present research.</td>
</tr>
<tr>
<td>2</td>
<td>Literature Review</td>
<td>Investigation and analysis of the pharmacovigilance domain.</td>
</tr>
<tr>
<td>3</td>
<td>Methodology of Research</td>
<td>Research methodology applied in the present research</td>
</tr>
<tr>
<td>4</td>
<td>The Knowledge Discovery Cube (KDC) Framework for pharmacovigilance innovation</td>
<td>Development of the Reference Framework for pharmacovigilance innovation</td>
</tr>
<tr>
<td>5</td>
<td>The ADVANCE case study</td>
<td>Operationalisation and empirical validation of the developed framework in the context of the ADVANCE project</td>
</tr>
<tr>
<td>6</td>
<td>Conclusions and suggestions for future work</td>
<td>Reflection on the research work, its achievements, limitations and future directions.</td>
</tr>
</tbody>
</table>
Chapter 2: Literature Review

“Analysis is the critical starting point of strategic thinking”

Kenichi Ohmae (1982), Japanese organisational theorist

Aim of this chapter is to explore the evolving landscape of public health and to provide an understanding of current practices and emerging paradigms that are relevant to medicines safety monitoring. This involves an analysis of both traditional methods and trends regarding technology directions that could influence pharmacovigilance moving forward. The latter are collected from recent publications regarding state-of-the-art technologies and current research directions. For the purposes of this investigation, relevant scholarly studies and reports were identified, addressing the topics of pharmacovigilance, healthcare, healthcare data. Furthermore, the macro-environment for global technological trends of relevance to this field were analysed, including contextual factors that condition technological developments. Discussion is outlined in three main parts, as follows: Firstly, the present state in pharmacovigilance is outlined, with a discussion of traditional methods of pharmacovigilance (Part A). Secondly, the way forward in pharmacovigilance is investigated (Part B). Thirdly, the emerging ecosystem paradigm in pharmacovigilance is discussed in detail (Part C). Finally, the information value-chain for health and medical research is analysed (Part D).

Part A is outlined in five sections. Section 1 provides an introduction into current post-marketing monitoring practices. Section 2 discusses signal generation within existing Spontaneous Reporting Systems (SRS). Other methods for hypothesis generation for signal generation are detailed in Section 3. Section 4 is dedicated to post-authorisation epidemiological studies that complement decision making, and Section 5 presents Benefit/Risk studies.

Discussion in Part B is outlined in four sections, as follows: Section 1 provides an introduction to foresight. Section 2 presents global technology trends of relevance to the pharmacovigilance sector. Section 3 focuses on global technology trends and relevant socio-economic factors that
may affect innovations. Section 4 presents innovative research practices and technologies in the field of pharmacovigilance.

Part C (The pharmacovigilance ecosystem paradigm) discusses the emerging paradigm of collaborative innovation in the pharmacovigilance ecosystem.

Part D undertakes an ethical investigation of the information value-chain for health and medical research.

Knowledge and insights generated, serve as basis for the extraction of requirements for the development of a comprehensive Reference Framework for pharmacovigilance innovation. The outcomes of Chapter 2 flow into Chapter 4.
Part A: Post marketing safety surveillance

1. Introduction

Part A provides an overview of established methods of pharmacovigilance: of the approaches and instruments used, their benefits and limitations. In the light of the limitations of pre-marketing clinical studies (WHO, 2002a; Striker & Psaty, 2004; Arona, 2012; Alomar, 2014), it is generally accepted that part of the process of evaluating drug safety needs to happen in the post-marketing phase, after a drug is approved by the health authorities and made available to the public, as many ADRs cannot be discovered prior to marketing (WHO, 2002a). This stresses the importance of the establishment of a mechanism for the continuous post-marketing surveillance of medicines. Monitoring the potential adverse effects of products already on the market is primarily a national activity that relies on spontaneous reports from patients and doctors (Hancher, 2010). A country’s pharmacovigilance system should incorporate activities and resources at the national and international levels (in the framework of the European Medicines Agency, the World Health Organisation etc.) and foster collaboration among a wide range of partners and organisations that contribute to ensuring medicine safety. The objectives of post-marketing safety monitoring are summarised by the WHO (2008) as follows:

**Table 4. Objectives of post-marketing safety monitoring**

- Identification of signals of serious adverse drug reactions following the introduction of a new drug or drug combination;
- Assessment of signals to evaluate causality, clinical relevance, frequency and distribution in particular population groups;
- Communications and recommendations to authorities and the public;
- Appropriate response/action in terms of drug registration, drug use and/or training and education for health professionals and the public;
- Measurement of outcome of response or of action taken (e.g. reduction in risk, improved drug use, or improved outcome for patients experiencing a detected adverse reaction).

Post-marketing safety surveillance can employ several methods (Aronson et al., 2012). Vray et al. (2005) state that pragmatic, postmarketing trials and observational studies are the reference methods used to define the population affected the efficacy and safety of the drug in a real situation and its usefulness for public health. Post licensure drug safety surveillance can be characterised as passive or active (WHO, 2008):
Chapter 2: Literature Review

• **Passive pharmacovigilance** relies mainly on voluntary reports of ADR collected from healthcare professionals and patients, and represents the most common form of pharmacovigilance. This means that no active measures are taken to look for adverse effects other than the encouragement of health professionals and others to report safety concerns.

• **Active pharmacovigilance** means that active (or proactive) safety surveillance measures are taken to detect adverse events. This includes specific studies and targeted follow-up actions (e.g. direct patient feedback collection). The most comprehensive method is cohort event monitoring (CEM), an example of which is the Prescription Event Monitoring (PEM) in England. Other methods used include the use of registers, record linkage and screening of laboratory results in medical laboratories.

Examining the merits of the two approaches, Bakare et al. (2011) argue that spontaneous surveillance is suitable for detecting low incidence adverse events, as it studies large numbers of patients, while active surveillance of cohorts or through the use of registries can be used to study special populations. Overall, passive surveillance systems are considered to capture only a fraction of all ADRs (Hazell & Shakir, 2006; Bäckström et al., 2004; Fletcher, 1991; Moore et al., 1998; Alvarez-Requejo et al., 1998). Given the limitations of passive surveillance, active pharmacovigilance methods are an important adjunct to evaluation of passively reported ADRs (Wiktorowicz et al., 2000). In their review of existing systems that collect data for drug safety evaluation, Huang et al. (2014) identified nine systems that qualify as active surveillance systems, among which the Vigilance and Risk Management of Medicines (VRMM) Division and the Drug Safety Research Unit (DSRU) in the UK. These surveillance systems mostly use administrative claims or EHRs and employ either a common data model or a centralised model to access this data. Depending on the ADE report collection scheme, pharmacovigilance systems falls into two categories (Gliklich et al, 2014), systems that employ intentionally solicited or unsolicited events. The former describes systems that rely on uniform information collection. This is the case of reports that are actively sought from studies or organised data collection systems. The latter rely on ADE information that is volunteered or noted in an unsolicited manner. This is the case of spontaneous reports.

**Post marketing risk management**

Strict regulations apply for the marketing phase of medicines. If the overall benefit to risk balance of a drug is judged to be unacceptable, even after the effect of any appropriate mitigating
action is taken into account, the medicinal product should be withdrawn from the market. (EC, 2011). In Europe, the European Medicines Agency requires pharmaceutical firms to have risk management plans (RMP) when they submit an application for marketing authorisation, providing detailed information about the drug's safety profile, risk factors for adverse reactions, and plans for studies to further investigate its safety and efficacy. Similarly, in the USA, the FDA requires from developers of certain prescription drugs and biologics to submit a risk evaluation and mitigation strategy (REMS), i.e, a risk management plan for the post-licensure phase of the drug. Risk mitigation measures (elements to assure safe use, ETASU) include: training programs for healthcare practitioners and/or patients, patient monitoring, additional tests etc.

Section 2 discusses signal generation within existing Spontaneous Reporting Systems (SRS). Other methods for hypothesis generation for signal generation are detailed in Section 3. Section 4 is dedicated to post-authorisation epidemiological studies that complement decision making, and Section 5 presents Benefit/Risk studies.

2. Spontaneous Reporting

In the past decades, Postmarketing Spontaneous Reporting Systems (SRSs) for suspected ADRs have been the most common method for the detection safety signals and the assessment of benefit, harm, effectiveness and risk of medicines (WHO, 2006). Arora (2012) defines SRSs as “voluntary passive surveillance systems that collect reports of suspected adverse events reported by Healthcare professionals (HCPs) and product consumers”. SRSs enable medicines to be monitored throughout their lifetime beyond licensure and are particularly useful in identifying rare or delayed reactions. The majority of existing pharmacovigilance SRSs maintain large databases for storing ADR reports and for signal detection. The SRS databases often contain millions of reports and have effectively contributed to the detection of many ADR signals. There exist several spontaneous reporting databases, operating on national and international level. In the UK, the primary system for reporting suspected ADRs is the ‘Yellow Card Scheme’ (YCS) (Davis & Raine, 2002; British Medical Association, 1996, 2006; Metters, 2004). Prominent SRS databases are detailed in Table 5.
Table 5. Selected Spontaneous Reporting Systems

<table>
<thead>
<tr>
<th>SRS</th>
<th>Country</th>
<th>Centre of Operations</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event Reporting System (AERS)</td>
<td>USA</td>
<td>Food and Drug Administration (FDA)</td>
<td>The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. (FDA, 2016b)</td>
</tr>
<tr>
<td>Vigibase/ Uppsala Monitoring Centre</td>
<td>all</td>
<td>World Health Organisation (WHO)</td>
<td>Established in 1978, the principal function of the Uppsala Monitoring Centre (UMC) is to manage the WHO Programme for International Drug Monitoring. UMC maintains VigiBase, the international database of global Individual Case Safety Report (ICSR) reports received from National Centres participating in the WHO Programme for International Drug Monitoring. (Lindquist, 2008).</td>
</tr>
<tr>
<td>EudraVigilance</td>
<td>EU</td>
<td>European Medicines Agency (EMA)</td>
<td>EudraVigilance (European Union Drug Regulating Authorities Pharmacovigilance) EudraVigilance is the system for managing and analysing information on suspected adverse reactions to medicines which have been authorised in the European Economic Area (EEA). The European Medicines Agency (EMA) operates the system on behalf of the European Union (EU) medicines regulatory network (EMA, 2016a).</td>
</tr>
<tr>
<td>Yellow Card Scheme (YCS)</td>
<td>UK</td>
<td>Medicines and Healthcare Products Regulatory Agency’ (MHRA) and the ’Commission on Human Medicines’ (CHM).</td>
<td>The Yellow Card Scheme is the UK system for collecting information on suspected adverse drug reactions (ADRs) to medicines. (MHRA, 2016b). YCS was originally founded in 1964. Yellow cards (YCs) are submitted voluntarily to the MHRA and then distributed to one of five Regional Monitoring Centres (RMCs) and entered into the Adverse Drug Reactions On-Line Tracking system (ADROIT) database.</td>
</tr>
</tbody>
</table>

SRSs collect reports from marketing authorisation holders (MAHs), healthcare professionals and patients (consumers) (Blenkinsopp et al, 2007; Avery et al., 2011; Hazell et al., 2013). The need to empower patients to report their side effects has been acknowledged by the EU (European Commission, 2008). The new EU pharmacovigilance framework expanded spontaneous patient reporting to include direct patient reporting as a means to complement reports from healthcare professionals. Reporting channels are also expanding. In the US, MedWatcher allows patients and physicians to submit ADR reports for medical devices, drugs, vaccines, and biologics via Internet or using mobile applications (Bahk et al., 2015). In Europe, the WEB-RADR project is researching direct patient reporting of ADRs using mobile applications (Ghosh & Lewis, 2015).
According to Santos (2015), the combination of reports from healthcare professionals with first-hand information from patients is of great added value because it increases chances to identify new safety issues. Suspected ADRs are typically coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adherence to a common coding scheme allows the analysis of data across SRSs, making it easier to share data for products used in many countries. In the EU, ADR information collected in national SRSs is aggregated by the EMA. National officials come together in the EMA to jointly take decisions on the safety of drugs on the market.

The principal advantage of SRSs is their comprehensiveness: spontaneous reporting is a mechanism that covers all drugs throughout the whole of their lifetime, incorporating prescribers, dispensers, and patients (Strom, 2006; Mann & Andrews, 2007). Although SRS represent the primary source for drug safety signal detection these systems have inherent limitations. The principal factors conditioning the effectiveness of a SRS are the reporting frequency (number of reports collected) and the quality and timeliness of reporting. Ideally reports should include patient characteristics and details about the drug use (age, gender, health conditions, concomitant medicines, onset time of event, date of prescription, dose, indication for prescription, and if the product was continued after the event or not). Complete information is not always available and follow up reports may be required. Furthermore, with ADR reports being unsolicited, SRS depend on the goodwill of reporters to report adverse events, and their ability to recognise that these are related to the drug. Basch (2013) notes that many adverse reactions are missed due to lack of interest, willingness, availability, or awareness of stakeholders to report. The report originator is also an important parameter (Strom, 2004). A comparison of reports submitted by patients and healthcare professionals has revealed significant differences in reported information (van Hunsel et al., 2009, Rolfes et al. 2015), raising questions about the role of patients in pharmacovigilance. At the same time, the majority of the ADRs signalled by the existing methods applied to SRS databases do not correspond to ADRs. Strom (2006) describes the system’s underascertainment (not recognising an event is due to a drug), overascertainment (erroneously ascribing an adverse event to a drug) and underreporting as its major flaws. Underreporting can be attributed to several factors that relate to the ambiguity surrounding ADR identification (Peddie et al., 2015), namely failure to associate the adverse event with the drug or to understand that the adverse event should be reported (Mittmann et al, 2004; Mann & Andrews, 2007; Sethi, 2014). According to Pal et al. (2013) SRS are the easiest to
establish and the most economical to operate, but suffer from poor-quality and incomplete reports, and underreporting. It is difficult to estimate rates and frequencies of ADRs through spontaneous reporting. Mann and Andrews (2007) note that the data provide only a ‘numerator’ (the number of reports of each suspected reaction), making the calculation of reliable rates impossible. Analysing the experience from several pharmacovigilance systems in Europe that have introduced direct patient reporting, Santos (2015) stresses the importance of awareness-raising and knowledge creation activities, patient usability and convenience, reporting language and forms. Increasing the effectiveness of SRS calls for an active and reliable reporting culture, and the education and encouragement of reporters (Srba et. al., 2012, MHRA, 2014).

2.1 Signal generation using spontaneous reports

Altogether, the process of identifying an ADR (establishing a causal relationship between a drug and an adverse medical event) comprises three stages: signal detection, refinement and evaluation (Platt & Carnahan, 2012; Robb et al. 2012). First, all reported drug-medical event pairs are analysed to highlight possible ADR associations (signal generation) and then the magnitude and clinical significance of a suspected association is evaluated (signal refinement). Finally, a formal epidemiological analysis is implemented to more definitively establish or refute causality (signal evaluation).

2.1.1 Signal detection

Hauben & Reich (2005) stress that a principal concern of pharmacovigilance is the timely identification of adverse drug reactions that are novel in terms of their clinical nature, severity, and/or frequency. SRS essentially collect data that allow scientists to constituting hypothesis that relate to the rational and safe use of a medicine. Because of existing limitations, adverse event reports are primarily useful for hypothesis generation, rather than hypothesis testing (Kennedy et al., 2000). Rather than certainties, scientists extract from SRS signals, described by Meyboom et al. (2017) as consisting of “a hypothesis together with data and arguments.” A signal is generally described as reported information on a possible causal relationship between an adverse event and a drug, the relationship being previously unknown or incompletely documented (WHO, 2002a; 2002b). The aim of signal detection is to promptly detect any possible unwanted effect associated with a medicine or to detect a change in the pattern or frequency of ADRs already known to be associated with a drug (MHRA, 2016a). A signal is not
a confirmed adverse reaction; however it represents an unusual occurrence, not included in the safety profile of the drug, and as such requires further investigation. Every new ADR report received could potentially contribute to a new signal. Usually more than a single report is required to generate a signal, depending upon the quality of the information and the seriousness of the event. In the case of rare adverse reactions, a small number of suspected cases associated with a single drug is sufficient for signal generation, as this is unlikely to be a chance phenomenon (Shakir SA & Layton, 2002). The following table summarises the key attributes of a signal (Hauben & Aronson, 2009) and the criteria for further investigation (Van Puijenbroek et al., 2001).

Table 6. Signal attributes and investigation criteria

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Description</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data evidence</td>
<td>It is based on information from one or more sources (including observations and experiments), suggesting an association (either adverse or beneficial) between a drug or intervention and an event or set of related events (e.g. a syndrome).</td>
<td>Strength of a signal (whether the data for each report indicates a strong association between the drug and the adverse effect).</td>
</tr>
<tr>
<td>Novelty</td>
<td>It represents an association that is new and important, or a new aspect of a known association, and has not been previously investigated and refuted.</td>
<td>whether or not the issue is New (the phenomenon has not been observed before with the drug under investigation) Importance as judged by the seriousness of the reaction and severity of the cases</td>
</tr>
<tr>
<td>Action</td>
<td>It demands investigation, being judged to be of sufficient likelihood to justify verification and, when necessary, remedial actions.</td>
<td>The potential for Preventive measures by the regulatory authorities to protect future patients.</td>
</tr>
</tbody>
</table>

There are many methods for signal detection. The ultimate aim is to detect possible drug safety issues as soon as possible so that prompt action can be taken to protect public health.

Qualitative Signal Detection Methods

Early methods of signal detection involved case-by-case analysis of each ADR report to determine whether contribute to a new signal (Egberts et al., 2002; Bate et al., 2002). Nowadays, this approach is considered unrealistic due to the large volume of ADR reports generated. Instead, quantitative measures for signal detection have been developed to help identify signals to be explored in subsequent controlled studies. Egberts et al. (2002) underline that adequate signal detection solely based on the human intellect is becoming time consuming given the...
increasingly large number of data, as well as less effective, especially in more complex associations such as drug-to-drug interactions, syndromes and when various covariates are involved.

**Quantitative Signal Detection Methods**

There exist various quantitative approaches; however, they all build on the principle of disproportionality (Egberts et al., 2002). Statistical methods are applied on suspected drug-reaction combinations in the database, and each combination is assigned a **disproportionality score**. Analysis examines whether the observed ratio of reports, linking a particular event with the drug, is higher than expected, with ‘expected’ being the ratio of a particular event to the total number of events in the database as a whole (van Puijenbroek et al., 2002). The absence of denominator in disproportionality calculations limits the method’s ability to generate safety signals and put signals into context. For putting a newly identified risk into perspective, it is important to quantify it in terms of incidence (CIOMS, 1998). The possible denominators are Number of individuals/patients who are/were exposed to the health product, number of patients exposed to the duration of drug and number of unique individuals dispensed the drug (CIOMS, 1998). Nonetheless, due to insufficient details and underreporting in SRS, it is very difficult to identify the denominator (Arora, 2012).

Disproportionality methods can be applied for the creation and validation of a pharmacological hypothesis about the mechanism of occurrence of ADRs or to identify rare and/or nonspecific ADRs in a timely manner (Montastruc et al., 2011; MHRA, 2016a). However, the use of disproportionality to automatically generate signals on drug safety is not always effective, since the method does not include any recognition or adjustments for pharmacological, biological, clinical or demographic determinants of adverse drug reactions.

**Data Mining**

Although the methodologies used for pharmacovigilance have remained largely unchanged during the past decades, automated signal generation building on **data mining algorithms** is a growing field. Data mining techniques allow for the extraction of useful information from massive real world observational data sets (Smyth, 2000) and as such can play a significant role in the analysis of spontaneous reports (Bate & Edwards, 2006). Only a limited number of the potential signals identified are important enough to require further investigation. Studies have
demonstrated that data mining can lead to the detection of “surprise reactions”, i.e. adverse reactions that may be discounted during manual review (Hauben et al., 2007). There is no single data mining method or tool for pharmacovigilance Wilson et al., 2004; Hauben et al., 2006a; Hauben et al., 2006b; Hauben &.Reich, 2004; Bate et al., 1998; Bate et al., 2002a; Bate et al., 2002b; Harvey et al., 2004). Evaluation results are conditioned by the theoretical basis and limitations of the method employed, as well as by the inclusiveness of the reference event database employed. It mainly consists on ascertaining false-positive rates of signals of disproportionate reporting (SDRs), and on assessing the overlap among SDRs detected by the different algorithms. Published evaluations of these techniques are usually limited to large regulatory databases, and performance characteristics may differ in smaller safety databases of drug developers.

Spontaneous reporting has clear strengths (Rawlins, 1988; WHO, 2004; Bate & Edwards, 2006) and well known limitations. Caution is needed when evaluating data originating from spontaneous reports, since often their clinical quality is limited. Case reports can include up to 200 fields of information. Reporting rates are low and variable and the quality of the reports can be poor (Noren et al., 2005), also depending on the report sender. For example, the EMA only allows reporting by healthcare practitioners, which typically results in more complete clinical information being collected, as opposed to USA where reporting is open to anyone. The currently used coding schemes are conceptually limited, the data structures deal badly with drug combinations, and the analysis tools have never been properly benchmarked (Bate et al., 1998).

Furthermore, feedback is often collected in non-systematic natural language narrative text forms. In the UK, the Yellow Card Scheme, combines keyword and text entry fields in a semi-structured reporting form (e.g. textual descriptions are required to “describe the reaction(s) and any treatment given” and to provide “additional relevant information” about the case treated).

Although the adoption of a standardised coding scheme (defined as “a classification, nomenclature, terminology, vocabulary or other set of codes that can be used to identify medical artefacts uniquely and unambiguously” (Cimino, 1996) would facilitate the systematic organisation of data, this would eventually limit the clinician’s freedom in documenting their opinion, which could result in important pieces of information not being recorded. In the past, scholars have proposed the application of data mining techniques for anticipating user input requirements with view to making an intelligent interface to support efficient data entry in the
different contexts this might occur (Spenceley & Warren, 1998). Any attempt to **standardise the reporting method** would run the risk of not providing adequate detail for indexing, which could result in important pieces of information not being recorded. Cimino et al. (1989) reviewed several controlled vocabularies designed for clinical use and outlined key qualities necessary for an effective clinical vocabulary: domain completeness, non-ambiguity, non-redundancy, explicit representation of synonyms, multiple classification of terms, and explicit relationships among terms. Currently classification systems are used to code terms in one-dimensional hierarchical structures, while ontologies offer multi-dimensional representations of the medical world, with concepts being linked to each other via several types of relationships. In the past, considerable domain knowledge has been assembled and documented in a wide variety of classifications, methodologies, terminologies, and controlled vocabularies for epidemiological, statistical and other purposes (e.g. ICD, SNOMED, Read, Gabrieli, MeSH, ICPC, UMLS etc). The domain knowledge thus documented includes diseases, disorders, symptoms, and medical signs, as well as health procedures and interventions carried out by medical professionals, medication substances, topographies of organs and parts of the human body. Yet, no scheme can be considered fully comprehensive (Campbell & Payne, 1994) and although the importance of a “common medical language” is widely acknowledged, this does not imply that all (people and systems) have to commit to one common terminology. In practice no single, common medical terminology can ever exist and despite training, it is practically impossible to make physicians employ terms always and ever in the same way (WHO, 2006). Instead, “communication” and “transferability” of knowledge is required (Pappa et al., 2006).

In light of the above, it would appear that the simplest and most effective method for detecting signals of adverse events remains the **crude inspection** of lists of spontaneously reported drug-event combinations, as the key element in the process is always the tacit knowledge of involved scientists and healthcare practitioners (i.e. their scientific **expertise** and clinical **experience**), which is very difficult to reproduce in a document or capture in a database. This knowledge that is deeply rooted in an individual’s actions and experiences ideals, values or emotions, can be expressed in terms of employee skills, problem solving abilities and mental models (Nonaka & Takeuchi, 1995). Fractions of the knowledge of experts can be captured in the form of **narratives** or can be embedded in **routines, processes** and **practices**. Thus, it is difficult for any strict codification scheme to fully capture and express expert knowledge or even to successfully
replace textual reports. Davenport and Prusak (1998) state that “the challenge to codifying knowledge is to leave its distinctive attributes intact, putting in place codification structures that can change as rapidly and flexibly as the knowledge itself.” Overall, the context in which pharmacovigilance initiatives need to navigate is one where (a) no single, common medical terminology will ever exist; (b) medical terminology cannot fully capture the essence of a free-text medical report (i.e. expert knowledge); and (c) despite training, it is practically impossible to make physicians employ terms always and ever in the same way.

In view of the growing interest in improving quantitative signal detection methods in spontaneous reporting, clinical trial and electronic health records databases, the Innovative Medicines Initiative PROTECT project has formulated 39 recommendations that mainly aim to address existing limitations in terminology and coding, and statistical analysis methods (Wisniewski et al., 2016).

2.1.2 Signal validation: Assessment of causality

Signal validation is the process of evaluating the detected signal to determine potential causality and justification for further analysis. Once a signal has been identified, investigations are necessary to refute or confirm a causal relationship between the drug and reported reaction (i.e. that the drug caused or contributed to the effect) and identify possible risk factors contributing to the reaction. Causality assessment refers to the process of determining etiologic and pathophysiologic evidence for an adverse event caused by a given drug. Since in medicine it is usually nearly impossible to make an affirmatively claim that a drug has caused a reaction (Rothman & Greenland, 2005), the result of an assessment is more often a ‘probability of causality’. Signal validation considers the likelihood of the association, investigates potential risk factors and attempts to quantify the risk (estimate the frequency of occurrence).

The first step consists in confirming the proper use of the drug. Subsequently the likelihood of other potential causes of adverse reaction needs to be investigated (e.g. adverse event due to concomitant drugs). Once other potential causes have been dismissed, additional investigation of the ADR is required (monitoring the patient's status while discontinuing the drug, reducing the dose or restarting the treatment to observe potential recurrence of the phenomenon) to assess how likely it is that this medication is the cause of this problem in this particular patient.
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During this assessment data from other sources may also be referred to, for example case reports in the literature, pre- and post-marketing clinical trials, epidemiological studies, record-linkage databases, data from other drug regulatory authorities etc. Relevant guidance is provided by regulatory organisations (e.g. ICH).

Establishing the causal relationship between the administration of the drug and the occurrence of the adverse event represents one of the key challenges in pharmacovigilance. **Causality assessment** mainly aims at excluding reports of adverse reactions that can be attributed to other causes (improper use of the medicine, parallel use of other medicines etc.) or known contraindications. The key question to be answered is: how likely is it that this medication is the cause of this problem in this particular patient? This relates to establishing an association in time between drug consumption and event (temporal relation), confirming the medical plausibility of the case at hand (coherency) and excluding other potential causes also in relation to previous knowledge of side effects. Traditional statistical methods cannot provide insight on causal relationships and instead causality inference relies mainly on the clinical judgment of an expert's panel (global introspection). It is considered a difficult process due to the complex nature of adverse events, multiple therapy and individual clinical variability (Stephens & Talbot, 1985).

Approximately 30 decisional algorithms (**Causality Assessment Scales**) have been proposed for causality assessment in the recent decades, in the form of questionnaires, decisional tables etc., for the purpose of establishing a standardised and less subjective procedure for causality evaluation (e.g. the Naranjo scale (Naranjo et al. 1981), the Bradford-Hill criteria (Hill, 1965), the WHO assessment scale etc). The Bradford Hill considerations include strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence and analogy. The Naranjo scale method is applied for estimating the probability of adverse drug reactions. Its main underlying conditions include challenge, dechallenge, rechallenge, previous bibliographic descriptions and etiologic alternatives. While these approaches offer a systematic approach for using scientific judgment to infer causation, the outlined "criteria" represent important "viewpoints", but are neither necessary nor sufficient for causation (Phillips & Goodman, 2004) and their application varies from a counterfactual consideration (Höfler, 2005).

Rothman & Greenland (2005) note that causal inference in epidemiology is better viewed as an exercise in measurement of an effect rather than as criterion-guided process for deciding whether an effect is present or not. Furthermore, comparative studies have revealed low rates of
agreement between algorithms and expert panel global introspection in terms of the decisions reached.

ADR reports document adverse events, capturing data elements relevant to causality assessment. Several confounding factors exist that may be linked to an adverse event, such as concomitant medications, patient demographics, patient medical histories, etc. Figure 1 maps ADR-related information items that need to be examined, in order to determine causality.

![Figure 1. Concepts investigated for causality assessment](image)

Each ADR report submitted links an adverse reaction that has occurred to a certain patient, to a specific suspected drug. Each patient has their individual clinical characteristics (age, sex and medical history), may have received other drug therapy in the past and may be receiving additional drugs at present (in parallel to the one suspected for causing the adverse event). All drugs are administered to the patient for a certain purpose (drug indication, usually recorded using the MedDRA terminology), in a certain form and in a certain dosage. The drugs have strict administration guidelines and known contraindications (i.e. a record of specific cases or situations in which the drug should not be used, because it could be harmful to the patient). All confounding factors need to be taken into consideration when assessing ADR reports.

Advances in informatics-driven approaches can enhance the effectiveness of signal detection and contribute valuable insight towards the establishment of causal associations. This includes
the in-depth investigation of confounding factors. For instance, Ai et al. (2015) reviewed recent advances in informatics-driven approaches to reveal drug–drug interactions (DDI) making use of knowledge from diverse information sources (scientific articles, adverse event reports, clinical texts etc.).

While spontaneous ADR reporting is the more diffused method for drug safety signal detection, several other methods are also utilised for hypothesis generation.

3. Other methods for hypothesis generation

Several methods for the identification of potential ADRs have emerged, building on the analysis of data evidence collected for other purposes. This includes Prescription event monitoring (PEM) systems, General Practice Research Database (GPRD) and other clinical and administrative health registers.

3.1 Prescription Event Monitoring (PEM)

Prescription Event Monitoring (PEM) is a system that collects all prescriptions issued for particular drugs over a specified period of time and the patients who were issued these prescriptions are subsequently tracked to look for any untoward events (Shakir,2005). PEM is a method for hypothesis generation in the post-marketing phase that also provides opportunities for quantitative analyses and comparative studies of potential drug safety issues. This method is applied extensively in the UK (Inman, 1981) and in New Zealand (Harrison-Woolrych & Coulter,2007). In the UK, PEM is implemented by the Drug Safety Research Unit (DSRU), particularly for the collection of safety data on newly marketed drugs. Whenever a general practitioner issues a prescription and submits it for claims reimbursement, an electronic copy is transmitted to the DRSU. The DRSU requests prescribers of target medicines to voluntarily complete a ‘green card form’ questionnaire for each patient detailing any ADR following the prescription of newly marketed drugs. In New Zealand, the Intensive Medicines Monitoring Programme (IMMP) uses PEM information for the organisation of prospective observational cohort studies of selected new drugs. The cohorts are established from prescription data received from hospital and community pharmacies. Questionnaires are sent to the prescribers at regular intervals following receipt of the pharmacy printouts requesting information on any adverse events that have occurred since the most recent prescription (Heeley et al., 2002)
Prescriptions are useful for providing exposure data, i.e. for identifying patients who have been exposed to the drug. “Green cards” collect information on the outcome of exposure during a certain period. This includes all events and not only suspected adverse drug reactions. The collected PEM data contains details of the patient, duration of therapy and any notable events. In theory, the combined use of prescriptions and green cards can provide an indication of both the numerator and the denominator to apply disproportionality analysis. PEM can provide an estimate of event incidence over different time periods. The method resembles a non-interventional cohort study. The sample of patients identified might be representative geographically and in terms of population (Rawson, 2016) and incidents can be detailed further in relation to age, sex, pregnancy status and duration to onset. PEM has thus many potential applications, including various comparative studies (e.g. comparisons between drugs). A known limitation of the approach is the low return rate of green care reports and also the limited duration of the follow-up period (Mann & Andrews, 2007).

Current media

A variation of the method is Modified PEM (Mod-PEM), i.e. PEM studies that use follow-up questionnaires specific to the product being investigated. The aim is to capture detailed information regarding the safety profile of the product and the patient’s overall health, while a particular drug is prescribed.

3.2 Health registers and Observational databases

Health and other registers collecting longitudinal medical records and information are also routinely employed for the purposes of various studies (Ferrajolo et al., 2010) and are potential data sources for pharmacoepidemiologic studies (Strom, 2005). Currently used databases include general practitioners’ electronic medical records as well as administrative/claims healthcare databases which are, respectively, used for registering clinically relevant information of patients during routine care and for documentation of healthcare services provided to citizens for reimbursement reasons (Trifirò & Sultana, 2016). While information is collected irrespective of any research purpose, secondary use of these data sources allows for the evaluation of safety outcomes for a number of medicines (Magro et al., 2016). On the other hand, inability to collect or access longitudinal data can lead to stagnation in pharmacovigilance research. For example, this is the case of Germany, where the establishment of large longitudinal databases was not
promoted and the use of administrative healthcare data for pharmacovigilance purposes is severely restricted by the law (Douros et al., 2016).

In the UK, the General Practice Research Database (GPRD, www.gprd.com) operated by the Medicines and Healthcare products Regulatory Agency (MHRA) collects longitudinal medical records from primary care. The UK has a gatekeeper approach to healthcare and a patient’s GP has the overall responsibility for patients, also after referrals (Wikström, 2013). As a result, the GPRD is the world's largest computerised database of anonymised, longitudinal medical records from primary care and is also linked with other healthcare data. The large population covered, the long follow-up period and the amount of information that can be accessed either directly or indirectly make the GPRD of particular value for pharmacovigilance (Gini et al., 2013; Price, 2016). Collected information includes patient demographics and detailed data about medicines therapies and their effects (including prescribed drugs, laboratory data, coded disease data, and data on consultations). The GPRD can thus support a large array of research services concerning many issues including drug safety outcomes, including the execution of case-control studies. For example, longitudinal database studies have been used to investigate even rare adverse events potentially associated to psychotropic drugs (Trifirò & Sultana, 2016) and the association between the use of NSAIDs and myocardial infarction (Rainsford, 2012). A similar scheme is maintained by The Medicines Monitoring Unit (MEMO), an independent research unit established by the University of Dundee in Scotland that engages in retrospective hypothesis testing case-control and cohort studies using data sets derived from prescriptions, hospitalisations and death certificates. This is enabled by Tayside Scotland’s policy of assigning a unique identifying number to each patient registering for care by a general practitioner. By data mining all Scottish prescriptions of a selected drug, MEMO is able to conduct a range of investigations, including case-control and cohort studies, as well as epidemiological, economic, outcomes, genetic and drug utilisation studies. In the context of pharmacovigilance MEMO can support prospective Phase IV studies to identify and quantify ADRs in primary care. Other record linkage databases covering a range of topics (population-based registers of birth defects, childhood immunisation, etc.) are available in other countries (Arlett et al., 2005). Administrative data could also be used to identify patients presenting with adverse drug events for post-market surveillance, and to conduct research in patient safety and in drug safety and effectiveness. (Hohl et al., 2013). Several limitations exist. The challenges of confounding
control are particularly strong in studies using healthcare databases where information on many potential confounding factors is lacking and the meaning of variables is often unclear (Brookhart et al, 2010, Peddie et al., 2015). Rubin (2007) notes that confounding by indication is a pervasive issue in pharmacoepidemiological studies, namely, a problem that arises because the factors that influence the treatment choices made by clinicians and patients also typically affect outcomes. Similar to other types of confounding, confounding by indication biases the crude association between exposure and disease away from the true causal effect. The possibility of confounding by indication, protopathic bias, outcome, and exposure misclassification etc represents a limitation for studies that needs to be taken into account and addressed in the study design and analysis (Trifirò & Sultana, 2016). Operational challenges are also present with regards to the aggregation and processing of heterogeneous data. Gini et al. (2016) identified the following three steps in local data processing: (a) data reorganisation into a data structure common across the network; (b) derivation of study variables not present in original data; and (c) application of study design to transform longitudinal data into aggregated data sets for statistical analysis. Performing a comparison of relevant cases of empirical knowledge production from existing databases in Europe and the United States, Gini et al. identified several areas that would benefit from standardisation.

4. Post-authorisation epidemiological studies
Epidemiological studies are often organised to complement the findings of SRS data analysis. Following signal detection a variety of formal epidemiological studies can be undertaken to test hypotheses. These observational methods provide the most informative source of quantitative information on ADRs in the post-authorisation period. The principal methods are cohort studies and case-control studies. Mann & Andrews (2007) explain that cohort studies are the indicated method when the outcome has not been identified previously or when multiple outcomes are studied, while case-control studies are particularly useful for confirming rare ADRs, since this method can generate a lot of information from relatively few subjects.

4.1 Cohort studies
Cohort studies are generally used to compare exposed patients to unexposed patients, in order to determine the incidence and natural history of a condition. Cohort studies are observational.
Researchers identify a group of patients who are already taking a particular treatment or have an exposure, follow them forward over time, and then compare their outcomes with a similar group that has not been affected by this treatment or exposure. Cohort studies allow for events to be measured and compared in chronological order. Cohort studies may be prospective or retrospective. Mann (2003) notes that cohort studies are effective for the study of incidence, causes, and for prognosis. Their major disadvantage is the inability to exclude confounding and that cohort studies are susceptible to bias (due to selection of a non-representative sample or loss to follow up). This method has been applied widely to investigate suspected medicines risks, for example the potential of an association between the intake of vitamin D supplements and type 1 diabetes (Hyppönen et al., 2001), between cardiac arrest and ventricular arrhythmia in patients and antipsychotic drugs (Hennessy, et al., 2002), between measles, mumps, and rubella vaccine and autism (Taylor, et al., 1999).

4.2 Case-control studies
In case control studies, exposure/incident rates of patients who already have a specific condition are compared with exposure rates of people who do not have the condition (controls). Case-control studies determine the relative importance of a predictor variable in relation to the presence or absence of the disease (Mann, 2003). A significant excess in incidents in the case group to which the suspect drug is administered suggests that there may be an association with the drug. However, special attention is needed in case and control group definition and sample selection (Mann & Andrews, 2007). Case control studies are usually retrospective. For example, this method has been applied to examine whether aspirin represents a risk factor in Reye's syndrome, after fifty-six cases of the disease in school-aged children were reported in Michigan during the winter of 1979-1980 (Waldman et al., 1982). Children who developed Reye's syndrome were matched with a similar control group who did not. Results were compared and revealed a link between aspirin and Reye's syndrome. In addition to sampling bias, this type of studies is also susceptible to observation and recall bias.

4.3 Cross-sectional studies
These studies describe the relationship between diseases and other factors at one point in time in a defined population. Cross sectional studies lack any information on timing of exposure and outcome relationships and include only prevalent cases.
4.4 Randomised controlled trials

In Randomised Control trials (RCT) subjects are assigned by statistically randomised methods to two or more groups: intervention groups and control (no intervention) groups. Typically a group of patients is divided into two in strictly random order, with only one group being exposed to the treatment. Mann (2003) notes that in doing so it is assumed that all variables other than the proposed intervention are evenly distributed between the groups. This way some of the typical biases that exist in observational studies are minimised. RCTs are an important instrument during pre-marketing trials, used for the evaluation of safety and efficacy of new drugs. An RCT is a planned experiment and can provide sound evidence of cause and effect. However this method cannot effectively detect uncommon ADRs. In the post-marketing stage, the use of RCTs may be unethical: deliberately exposing people to a treatment to study its effect when the potential harmful effect of the studied drug is suspected. The use of cohort studies is recommended in this case.

5. Benefit/Risk studies

An important dimension of pharmacovigilance is the study of the drug’s benefits-to-risks balance (Stephens & Talbot, 1985; CIOMS, 1998). When the regulatory agency approves a drug it concludes that the drug's benefits outweigh its risks for the conditions outlined in the product label and that there is a public health benefit from the medication. The evaluation of the benefit to risk performance of a drug is an essential and on-going process during the entire lifecycle of a medicine. The overall purpose of ADR monitoring is to be able to provide information that can be used to assess the potential risks associated with the use of a drug against the expected benefit and inform decisions to protect patients’ health. The review of the benefits and the risks associated with a drug is called benefit-risk assessment (BRA), or benefit-risk balance, or benefit risk ratio evaluation (Murphy & Roberts, 2006; Curtin & Schulz, 2011). BRA essentially comprises the assessment and comparison of two dimensions: benefits and risks. The “benefits” dimension denotes positive outcomes or favourable effects associated with a medicine, and is measured in terms of therapeutic efficacy (i.e., the successful treatment of the condition for which the drug is indicated), improvement of quality of life or other pharmacoeconomic aspects. The “pharmaceutical risks” dimension denotes undesirable or harmful events related to a drug
therapy, and is measured in terms of the safety profile observed (including all recorded ADRs) and the potential risk of unobserved ADRs anticipated on the basis of the mechanism of action. Risks may be characterised according to different criteria to better describe their significance (e.g. common or rare; severe or merely irritating; documented or suspected etc.)

Benefit-risk assessment is essentially a qualitative assessment of quantitative data. Quantitative and semi-quantitative methods have also emerged (Walker et al., 2006; Mussen et al., 2007; Garrison et al, 2007; Brass et al., 2011; Curtin & Schulz, 2011). Mt-Isa et al. (2014) noted that there is not a ‘one-size-fits-all’ method, and a combination of methods may be needed for each benefit–risk assessment, as each methodology is associated with different limitations and strengths. The principal Benefit-Risk Evaluation frameworks as summarised by the Benefit-Risk Group of the IMI-PROTECT (Hughes et al., 2014) are:

**Table 7. Benefit-Risk Evaluation frameworks**

<table>
<thead>
<tr>
<th>Benefit-Risk Evaluation frameworks</th>
<th>Description</th>
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<tbody>
<tr>
<td>BRAT (Benefit-Risk Action Team)</td>
<td>BRAT standardises and supports the decision and communication of a benefit-risk assessment between pharmaceutical companies and the regulators through a 6-step process: define decision context, identify outcomes, identify data sources, customise framework, assess outcome importance, and display and interpret key benefit-risk metrics.</td>
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<tr>
<td>(Coplan et al., 2011; Levitan et al., 2011)</td>
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<tr>
<td>FDA BRF (Benefit-Risk Framework)</td>
<td>FDA BRF provides the “big picture” to “tell the story” by summarising evidence and addressing their implications for decision in a table for five decision factors: analysis of condition, unmet medical need, benefit, risk, and risk management.</td>
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<td>(Frey, 2012; Jenkins, 2010)</td>
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<tr>
<td>CMR CASS (Canada, Australia, Switzerland, and Singapore)</td>
<td>CMR CASS represents a quantitative approach for small regulatory agencies to address benefit-risk questions throughout product lifecycle and the post-approval assessment challenges. It has been superseded by COBRA (Consortium on Benefit-Risk Assessment) (CIRS, 2012) with a mission to develop a semi-quantitative framework to reflect the actual practice, but no details are yet published.</td>
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<td>(Walker, 2009)</td>
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<tr>
<td>SABRE (Southeast Asia Benefit-Risk Evaluation)</td>
<td>SABRE is a regional initiative in Southeast Asia aiming to promote better assessment of the benefits and risks of medicines. Details have not yet been published.</td>
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<td>(CIRS, 2012)</td>
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<td>UMBRA (Unified Methodologies for Benefit-Risk Assessment)</td>
<td>UMBRA works with the PhRMA BRAT, COBRA, and SABRE initiatives to establish a unified benefit-risk framework with common elements, currently addressed in a 4-stage, 8-step process: (1) framing the decision – decision context; (2) identifying benefits and risks – building value tree, refining the value tree; (3) assessing benefits and risks – relative importance of benefits and risks, evaluating the options; and (4) interpretation and recommendations – evaluating uncertainty, concise presentation of results, and expert judgement and communication.</td>
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<td>(CIRS, 2012)</td>
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Part B: The way forward in pharmacovigilance technologies

“Evolution is not a force but a process; not a cause but a law”

John Morley, British journalist, biographer and statesman

1. Introduction: Foresight

Technology is regarded as a main driving force in shaping the future of pharmacovigilance. This future is not predetermined, but can evolve in different directions, as technology evolution processes are usually nonlinear and unpredictable (Kostoff & Schaller, 2001). Technology foresight can provide inputs for the development of novel technological infrastructures and mechanisms for safety monitoring and for the formulation of methods and strategies to ensure the efficiency and effectiveness of these mechanisms. UNIDO(2005) defined Technology Foresight as the “process involved in systematically attempting to look into the longer-term future of science, technology, the economy and society with the aim of identifying the areas of strategic research and the emerging generic technologies likely to yield the greatest economic and social benefits”. Future oriented thinking is vital to allow for forward planning and/or policy activity to successfully harness emerging opportunities and to meet future challenges proactively. Foresight enhances such thinking by collecting anticipatory intelligence and linking it to today's decision making. This can involve gathering intelligence on possible longer-term developments and how these may transform the safety monitoring methods of today, or providing alerts on major future risks and opportunities. Technology foresight is a practical tool facilitating the identification of emerging and/or disruptive technologies, potential new applications to support the sector, business opportunities, strong and weak signals, etc.

Aim of forward looking in the present context is to explore methodological requirements to facilitate the development of capabilities for harnessing technology innovation, and to set priorities for innovation activities in pharmacovigilance methods. The goal is to identify the driving forces of today’s technical innovation and plan for long-term success.

The way forward in technology is shaped by current trends in global technological advancements, by technological research & development, as well as by technology maturity and the state of associated technologies and is strongly conditioned by macro-environmental factors referring to the social, legal, political, economic situation. In business, the value of forward
looking for strategic planning has long been recognised (Day & Schoemaker, 2006). In particular, companies operating in science-based and technology-based industries, which are subject to continuous and fundamental changes caused by science and technology innovations, need ways to anticipate future developments so that they can react to them in profitable ways (Cortada & Fraser, 2005). Senior leaders are expected to anticipate the future and provide direction, meaning and inspiration to their organisation. de Jong (2015) exalted the importance of **visionary capacity**, which he defined as consisting of two, independent, dimensions: the ability to recognise signs of change early and create a coherent understanding of the future and the ability to work through the complexity of this future. Navigating the future can be both a strategic and an operational challenge, as it can affect the organisation’s vision, mission, goals, and strategies and its operations (organisation and planning to accommodate emerging desired and undesired events).

In principle, the future can be anticipated by monitoring of industry trends and a continuous scanning of the environment for changes. This involves looking at the direction of important technological developments of today (trends and megatrends) and by sensing possible but improbable events (weak signals and wild cards), also identifying potential driving or hindering forces in the environment. A **trend** is a general tendency that is evident from past events, while a **weak signal** is essentially a sign of change that is not yet generally appreciated. A **strong trend** is a movement affecting a phenomenon in such a way that its development in time can be predicted (Kuusi, 1999). Weak signals are “imprecise early indications about impending impactful events” (Ansoff and McDonnell, 1990). A weak signal is a signal that is hardly perceivable at present but constitutes a strong trend in the future (Godet et al., 1994). Weak signals are currently small and seemingly insignificant issues and events, of very low estimated probability, but to which a high uncertainty is attached concerning the impact of those events and the trends that could develop afterwards (Mendonça et al., 2004; Hiltunen, 2008). Weak signal analysis can help predict **wildcards** that represent unexpected, high-impact events or phenomena (Hiltunen, 2008; Heinonen & Hiltunen, 2012). Forward looking allows businesses and organisations to assess the capabilities of emerging technologies, to develop a view of the trajectory of these technologies and their estimated performance over the coming years (forecast) and to analyse their potential impact on the sector (on methods and work processes, infrastructure needs and workforce requirements etc.). On the basis of these insights they can
develop options for applying these technologies in current and future business processes to generate value, in terms of both operating and strategic benefits. Finally, acting on these options, organisations can implement changes (redesign methods and work processes, restructure workforces etc) to accommodate innovation. Motorola invented *science and technology* (S&T) **roadmapping** as a method to support improved alignment between technology and product development, providing a structured visual depiction of strategy. Robert Galvin (1998), former Motorola chairman, stated that “a ‘roadmap’ is an extended look at the future of a chosen field of inquiry composed from the collective knowledge and imagination of the brightest drivers of change in that field. Roadmaps communicate visions, attract resources from business and government, stimulate investigations, and monitor progress”.

The **effect of the environment** in which innovation takes place also needs to be considered: paradigm shifts are conditioned by political, legal, economic and social (PESTLE) factors that are relevant to the macro environment. In principle, political factors denote how the government intervenes in the field. Political factors may represent influences, restrictions or opportunities, but they are not mandatory. Legal factors refer to established norms in the form of laws and regulations, which have to be complied with. Economic factors include economic indicators that greatly affect how businesses operate and make decisions. Social factors include the cultural aspects and health consciousness, population growth rate, age distribution, career attitudes and emphasis on safety. Examples of key factors are included in Table 8.

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<tr>
<th>Political factors:</th>
<th>Economic factors:</th>
<th>Social factors:</th>
<th>Legal factors:</th>
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<td>Trading policies</td>
<td>Access into the technological means</td>
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<td>Regulatory bodies and their processes</td>
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<td>Government changes</td>
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<td>Funding policies</td>
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<td>Governmental leadership</td>
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<td>Lobbying</td>
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<td>Foreign pressures</td>
<td>specific to relevant products/services</td>
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<td>Conflicts in the political arena</td>
<td>Disposable income</td>
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Chapter 2: Literature Review

This section focuses on trends analysis of critical emerging technologies, i.e. technologies that have a strong potential to influence the public health and life sciences sectors and help create efficiencies along the entire safety-monitoring continuum. These technologies may or may not have entered the sector yet. The aim is thus to develop a point of view about pharmacovigilance that extends beyond the immediate planning horizon. For this purpose, the technology environment was investigated for the identification of global technology trends (emerging generic technologies), including relevant expectations and considerations (Section 2), in order to shed light on the emerging digital health ecosystem (Section 3) and analyse the drivers of innovation in the field of pharmacovigilance (Section 4).

2. Global technology trends

Technology is a powerful force for change, gradually becoming an extension of the individual. Human interactions with technology continue to evolve, most visibly in terms of diversity and scale (Pontin, 2014). Digital technologies are transforming organisations, informing all aspects of business from ideation to delivery, and not solely operations and execution (Leonhard, 2013; Deloitte, 2016). ICT is becoming a key enabler of novel work methods, and a lever for new business models (Watson, 2009). Advances in artificial intelligence, machine learning, and natural user interfaces (e.g., voice recognition) are gradually enabling the automation of many knowledge worker tasks that have long been regarded as impossible or impractical for machines to perform (McKinsey Global Institute, 2013). Technology will continue to become more human-centric to the point where it will introduce transparency between people, businesses and things, with technology becoming more adaptive, contextual and fluid (Gartner 2016). In addition to new emerging technologies, transformational technologies of the past are coming together bringing new opportunities for transformation (World Economic Forum, 2015a; Chung & Kim, 2016; Schwab, 2017), with combinatorial innovations emerging at the intersection of distinct territories (IFTF, 2014).

The growth of mobile devices and the Internet of Things (Höller et al., 2014) represent a new catalyst for the explosion of data (Banerjee et al., 2016). By 2025, there will be 40 billion smart devices worldwide, and 77% of the global population will be connected across 100 billion connections Huawei (2017). Electronic devices are increasingly equipped with a multitude of sensors for sensing the environment around them (García et al., 2017). These Intelligent Products
are constantly monitoring the environment, and can react and adapt to it, also holding an active communication, in order to have an optimum performance (Ventä, 2007). This interconnection among smart objects can make them more intelligent and can also produce a wealth of data, to deliver new insights into the environment (Huawei, 2014; Garcia et al., 2017). The combination of sensors and wearables, increased connectivity, and improved data mining capabilities are creating a smart, connected world, where people, objects etc. are in continuous communication with one and other. The use of the Internet is growing in volume and expanding in scope (Meeker, 2016). Elon University and the Pew Internet Project (2014) envisage the year 2025 a time in which “global, immersive, invisible, ambient networked computing environment built through the continued proliferation of smart sensors, cameras, software, databases, and massive data centers in a world-spanning information fabric known as the Internet of Things”. Describing an all-encompassing vision for the future of connectivity, the internet of everything, AmpliFIRE pointed to the following four dimensions: things (Internet of Thing), services (Internet of Services), information (Internet of Information) and people (Internet of People). The Internet of Things (IoT) refers to the vision of a global, connected network of mobile devices, product tags, sensors and actuators, and mobile devices that interact so that people can achieve shared goals without direct user input. The Internet of Services relates to internet-scaled, service-oriented computing, such as cloud software (SaaS) or platforms (PaaS). The Internet of Information denotes the vision of sharing all types of media, data, and content across the internet in ever increasing amounts and combining data to generate new content. The Internet of People is about people to people networking, where users connect directly with other users privately and securely through their personal cloud. By and large, the boundaries between systems and users will become increasingly blurred. "Gartner's top 10 strategic technology trends for 2017 centre around the Intelligent Digital Mesh (Gartner, 2016c) a term denoting the dynamic connection of people, processes, things and services supporting intelligent digital ecosystems. Gartner’s vision for future intelligent connectivity includes advanced digital technology platforms, new types of service applications (cloud and serverless computing, containers, microservices) and fluid security architectures, supporting multiple users in multiple roles using multiple devices and communicating over multiple networks. The firm predicts that new platforms and services for IoT, Artificial Intelligence (AI) and conversational systems will be a key focus through 2020.
Technologies that could drive massive transformations and disruptions in the coming years, and are expected to particularly affect the domain of medicines safety monitoring include:

2.1 Digital forces of change

2.1.1 Big Data

Through the years knowledge has moved from paper-based knowledge management. Early computer systems served as memory devices, to digitalisation, and enabled productivity and efficiency improvements on work processes. Presently, the current trend of datafication that increasingly turns human life into computerised data, is transforming this information into new forms of value (e.g. UN Global Pulse, 2012; Huawei, 2014). The continuous growth in data production emphasises the question of how to best make use of it. Not only larger quantities of data are made available, but there exist many new data sources to extract knowledge from. The scale of datafication allows the extraction of new insights to create new forms of value. This trend creates a fundamentally new strategic landscape, challenging the very foundations of established methods and their ability to fully explore the new value creation space produced by datafication. It is not only about obtaining data, but also about making this data actionable, namely, by processing and analysing data, by making sense of the information and by using the knowledge produced in the right way.

These changes in society’s ability to collect information have already had profound effects on research and innovation, with a surge in e-knowledge that comes from analysing the data. In business, big data is of high economic importance, being viewed as a key enabler of competitiveness that underpins new waves of productivity growth, innovation, and consumer surplus, as long as the right policies and enablers are in place (Manyika et al., 2011; World Economic Forum, 2012). Personal data, in particular, is characterised as “the new “oil”, as “a valuable resource of the 21st century” (World Economic Forum, 2011). Gartner defines big data as “high-volume, high-velocity and/or high-variety information assets that demand cost-effective, innovative forms of information processing that enable enhanced insight, decision making, and process automation”. Big data is created digitally, produced passively, collected automatically, tracked geographically or temporally, and can be analysed in real-time (UN Global Pulse, 2012). The UNECE task team on Big Data (2014) proposed a taxonomy to classify big data as human-sourced information, process-mediated data or machine-generated data. Human-sourced information is mainly linked to Social Networks, which increasingly serve as
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records of human experiences. **Process-mediated data** relate to traditional business systems and websites, whose processes record and monitor business events of interest. **Machine-generated data** are derived from automated systems and the Internet of Things), i.e. from sensors and machines used to measure and record events and situations in the physical world. It is important to distinguish these different types of data sources, as each of them brings different considerations in terms of management and processing. Additional restrictions apply depending on whether data is personal or not. According to the World Economic Forum (2011) personal data refers to data (and metadata) that is created by and about people, and can be **volunteered** (created and explicitly shared by individuals), **observed** (captured by recording the actions of individuals) or **inferred** (produced from the analysis of volunteered or observed information). Big data’s potential is constantly increasing, and taking full advantage of it implies that organisations must incorporate analytics into their strategic vision (McKinsey Global Institute, 2016). The term **big data analytics** describes the process of collecting, organising and analysing large sets of data to discover useful information. Methods employed include data mining, text mining, data optimisation, predictive analytics, etc., and are bringing significant advantages compared to traditional statistical sampling. Large amounts of information can be collected from different sources and monitored continuously, in order to identify patterns and trends. Using big data analytics, new trends become self-explanatory, with the purposes and insights of the analysis being not prescribed but inducted from the flows of data itself. The method is therefore useful for the prediction and identification of the emergence and evolution of trends, which can be later analysed in a more traditional statistical way in order to identify their causes. However, there are several challenges inherent to big data analysis, namely the high volume of data, the different formats in which data is captured (both structured and unstructured data), other structural barriers that impede access and analysis (e.g. organisational data silos) etc.

**2.1.2 Cloud computing**

Cloud technology, allows for computer services to be delivered over a network or the Internet, with minimal or no local software or processing power required. The availability of virtual servers and processing capabilities over the internet, allow for advanced Internet-based services and enable a shift from technical infrastructure to ecosystem-enabling platforms (Gartner, 2016). Information sharing over the Internet will be so effortlessly interwoven into daily life that it will become invisible, flowing like electricity, often through machine intermediaries.(Elon University
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& Pew Internet Project, 2014). When our data leaves our personal devices, it often hits a cloud data centre where all that data is being stored, archived, backed up and even analysed to deliver us the services we rely on and ensure our digital records and files are safely stored and readily available.

2.1.3 Internet of Things/ Internet of Everything

The Internet of Things and pervasive connectivity are becoming a reality (Gubbi et al., 2013; Hansmann et al., 2013; Whitmore et al., 2014). According to a research report issued in 2014 by the Pew Research Center Internet Project, the Internet of Things will progress significantly between now and 2025. More and more things are being embedded with sensors and gaining the ability to communicate. Through the internet of things (IoT), physical objects are creating an information system (Daecher & Schmid, 2016). According to IoT expert Daniel Burrus (2014), the IoT is not just about sensors and machine-to-machine intelligence, or only about providing us with information. Value is created at the intersection of collecting data and leveraging it to drive action in real-time. The Internet of Things is expected to contribute significantly to the rise and growth of big data, with the rapid expansion of interconnected devices and sensors (Banafa, 2016). IoT is essentially the aggregation of a large number of already disruptive technologies, assembled in a novel way that combines the disruptive elements of those technologies and magnifies their effects. Smart tech, the Internet, social identity, big data, cloud, mobility, all these are affected by, and contribute to, the emerging IoT. Atzori et al. (2012) propose a vision for the Social Internet of Things (SIoT), defined as an IoT where things are capable of establishing social relationships with other objects, autonomously with respect to humans. In this way, a social network of objects is created.

2.1.4 The end of offline

The spread of the Internet and broadband networks will provide universal data access and advanced connectivity capabilities (Leonard, 2013). The opportunities and challenges resulting from amplified connectivity will influence nearly everything, nearly everyone, nearly everywhere. The current generation of mobile networks continues to transform the way people communicate and access information. Further developing and implementing technologies that enable true human-centric and connected machine-centric networks will come to redefine end user mobility along with the entire landscape of the global telecoms industry. The rapid global
uptake of smartphones has completely changed the way we communicate and use the internet. In this light, mobile networks are growing both in size and capabilities, and in significance. The promise of 5G Mobile Networks is to expand the possibilities of what mobile networks can do, and to extend upon what services they can deliver (Bojkovic & Milovanovic, 2016). Future networks will be characterised by user-centric network operation. Studies predict that, between 2020 and 2030, 5G wireless networks will reach maturity, which their features including super high data rate of 10 Gb/s per individual user, low latency and response times, high mobility, high energy efficiency, and high traffic density (Huawei, 2013; Chen, 2014; Chen et al., 2016). Breakthroughs in wireless network innovation are expected to drive economic and societal growth in entirely new ways.

2.1.5 Machine Intelligence

Machine intelligence, i.e. the ability of machines to learn and make their own decisions, is rising. Smart machine technologies will be the most disruptive class of technologies over the next 10 years due to radical computational power, near-endless amounts of data, and unprecedented advances in deep neural networks (Gartner, 2016). John McCarthy (1958) invented the term Artificial Intelligence to describe “the science and engineering of making intelligent machines”, i.e. of emulating human-like intelligence. He alluded the development of a system which is to evolve intelligence of human order. Artificial intelligence is about the intelligence exhibited by machines or software applications. Breakthroughs in the field are accelerating, with the development of computer software that has the capacity to imitate human ability to learn and adapt over time to changing circumstances (Michalski et al., 2013; Russell, & Norvig, 2016). Machines’ and systems’ understanding of human context, humans and human emotion is improving. A 2016 report by the US Office of Science and Technology Policy (OSTP) defines artificial general intelligence (AGI) or General AI as “a notional future AI system that exhibits apparently intelligent behavior at least as advanced as a person across the full range of cognitive tasks.”

Machine learning denotes the ability of computer systems to improve their performance by exposure to data without the need to follow explicitly programmed instructions (Pereira et al., 2015). The promise of Artificial intelligence is not that computers will start to think like humans, but rather represents efforts to automate tasks (automation of knowledge work) (Marcus, 2016). It demonstrates that given a large enough data set, fast enough processors, and a sophisticated
enough algorithm, computers can begin to accomplish tasks that used to be completely left in the realm of human perception. This also leads to simple context-aware interactions, to better understanding customers’ responses, (e.g. measure consumer sentiment for a new product) to complex dialoguing with customers, such as virtual assistants using natural language question and answering to respond to customer inquiries. The growth of data, combined with AI, allows for smarter decision making. Friess (2016) stresses that AI-enabled IoT applications allow for intelligent automation, predictive analytics and proactive interventions in several areas of day-to-day life. Bostrom (2014) proposed the concept of super-intelligence, which he describes as any intelligence that greatly exceeds the cognitive performance of humans in virtually all domains of interest, and identified three main areas of improvement: speed (systems that can do all that a human intellect can do but much faster), performance (systems that aggregate smaller intellects) and quality (systems that qualitatively improve on human reasoning and decision-making). Chalmers (2010) identified artificial general intelligence as a very likely path to superhuman intelligence, and an enabler of intelligence extension and amplification.

(i) AI and Advanced Machine Learning

Artificial intelligence (AI) and advanced machine learning (ML) are composed of many technologies and techniques (e.g., deep learning, neural networks, natural-language processing (NLP). The more advanced techniques move beyond traditional rule-based algorithms to create systems that understand, learn, predict, adapt and potentially operate autonomously. This is what makes smart machines appear "intelligent." Gartner (2016c) reports expert predictions about applied AI and advanced machine learning giving rise to a spectrum of intelligent implementations, in the area of both physical devices, and applications and services. "These implementations will be delivered as a new class of obviously intelligent apps and things as well as provide embedded intelligence for a wide range of mesh devices and existing software and service solutions." (Gartner, 2016c).Examples of intelligent devices include robots, autonomous vehicles, consumer electronics, while intelligent applications include virtual personal assistants, smart advisors etc. At present artificial intelligence is experiencing enormous growth. AI and machine learning can also encompass more advanced systems that understand, learn, predict, adapt and potentially operate autonomously. Machine learning programmed to recognise patterns of data and promote desirable outcomes, machine learning algorithms effectively rewrite themselves, a form of artificial intelligence (NESTA, 2016). Systems can learn and change future
behaviour, leading to the creation of more intelligent devices and programs. The combination of extensive parallel processing power, advanced algorithms and massive data sets to feed the algorithms has unleashed this new era. Rules-based systems allow using databases of knowledge and rules to automate the process of making inferences about information

(ii) Intelligent Applications

Intelligent applications, which include technologies like virtual personal assistants (VPAs), have the potential to transform the workplace by making everyday tasks easier (prioritising emails) and its users more effective (highlighting important content and interactions). However, intelligent apps are not limited to new digital assistants – every existing software category from security tooling to enterprise applications such as marketing or ERP will be infused with AI enabled capabilities. Using AI, technology providers will focus on three areas: advanced analytics, AI-powered, autonomous business processes and AI-powered immersive, conversational and continuous interfaces. By 2018, Gartner (2016c) expects most of the world’s largest 200 companies to exploit intelligent apps and utilise the full toolkit of big data and analytics tools to refine their offers and improve customer experience. Technologies stemming from artificial intelligence research are described as cognitive technologies (Schatsky et al., 2015). They are able to perform tasks that only humans used to be able to do. Examples of cognitive technologies include computer vision, machine learning, natural language processing, speech recognition, and robotics. Cognitive computing refers to systems that learn at scale, reason with purpose and understand natural language, allowing them to interact with humans more naturally. Cognitive systems learn and build knowledge and inferences from various structured and unstructured sources of information. They can “read” text, “see” images and “hear” natural speech. And they interpret that information, organise it and offer explanations of what it means, along with the rationale for their conclusions.

The collection of big data combined with AI, can produce intelligent automation, predictive analytics and proactive interventions. In organisations cognitive technologies can help automate work in two main ways: by augmenting workers or by replacing them (Schatsky et al., 2015). Cognitive technologies can support the automation of tasks at a scale that is impractical with conventional alternatives, to increase the speed and reduce the cost of operation. A third area of application of cognitive technologies is for the creation of insight. Natural language processing techniques make it possible to analyse large volumes of unstructured textual information.
Machine learning can draw conclusions from large, complex data sets and help make high-quality predictions from operational data. Many companies are using cognitive technologies to generate insights that can help reduce costs, improve efficiency, increase revenues, improve effectiveness, or enhance customer service. Gartner (2016c) predicts that over the next 10 years, virtually every app, application and service will incorporate some level of AI. This will form a long-term trend that will continually evolve and expand the application of AI and machine learning for apps and services. Recent innovations in the field of Artificial Intelligence include the development of the Watson supercomputer system by IBM for processing structured and unstructured data (Kelly & Hamm, 2014). Google is also investing in AI from image recognition to general intelligence, pursuing research projects such as Google Brain, which leverages the vast amounts of data the company collects to train its machines for better understanding of the world (Jones, 2014). Microsoft is active in the field of machine intelligence, through its Microsoft Adam project (Jorgensen et al., 2014). Facebook is using deep learning techniques to provide intelligent services to its social media users (Deng & Yu, 2014). At the same time, significant improvement in terms of computation and power efficiency in digital chips is achieved, increasing the processing speed of electronic devices.

2.1.6 Intelligent interfaces

Human Computer Interaction (HCI) is evolving rapidly (Jacko, 2012). Information interfaces are expected to advance further, especially voice and touch commands (Pew Center, 2014). Futurist Rohit Talwar (2016) predicts that, by 2025, the interfaces to all devices will be highly intelligent and adaptive, capable to learn from human behaviours and choices and anticipate their needs. If once the keyboard was an unresponsive piece of unintelligent hardware, the latest versions feature software touchscreens seemingly capable of anticipating and automatically responding to personal needs of the user. The development of contextually aware keyboards will draw on the sophistication of AI, and as it is built into widely used products like smartphones and used with regularity, will revolutionise data-input methods (Leonard, 2013). Language-independent interaction through the development of software that allows real-time translation between languages. The movement towards conversational interfaces is expected to accelerate (Gartner 2016b; Davenport & Ronanki, 2016). Presently, research on conversational interfaces is focused on chatbots, microphone-enabled devices and voice controlled systems (e.g. speakers,
smartphones, tablets, PCs, automobiles) and their use can range from simple informal, bidirectional text or voice conversations to more complex interactions. These systems enable users to interact with technology in natural language, through plain conversation.

(i) The Disappearing Interface

The digital ecosystem is constantly enriched with new types of devices and endpoints people can use to access applications and information, and to communicate or interact with other people or entities. Computers are increasingly found in clothes, glasses, and watches. From printable, bendable, stretchable electronics to breakthrough technologies that simplify our interaction with data and devices on the go, these innovations ensure that the way we think about computing will never be the same. According to Gartner, future interface systems will not use text/voice exclusively will but allow people and machines to use multiple modalities (e.g., sight, sound, tactile, etc.) to communicate across the digital device mesh (e.g., sensors, appliances, IoT systems) (Gartner, 2016c). Frost & Sullivan (2016c) foresee the coming of age of sentient tools, which represent the next stage of intelligent, aware, and social machines that are designed specifically to interact with people. Sentience is defined as the ability to perceive the world and to derive feeling or meaning from those experiences. Sentient tools are characterised by situational awareness, intelligence, social awareness and communication. The development of sentient tools involves the merging and overlap of a variety of technologies, such as computational, sensing, and communications technologies. In this context, computation will continue to move away from single-user desktop applications, toward a rich variety of novel forms and architectures. MIT researcher David Rose frames this shift as a transition from traditional computation toward a world of "enchanted objects" (Rose, 2014).

2.1.7 Devices: quantified self

Digital devices are getting smaller and smarter, while their capacity is constantly increasing. According to PSFK Labs (2014), most people use devices that constantly collect signals to quantify ourselves, document our lives, augment ourselves, create new realities, and express ourselves in new ways. There is a growing ‘datafication’ process with digital devices that surround us continuously collecting or generating data as a result of their every interaction (Rich & Miah, 2017). Technology enables extended data acquisition on aspects of a person's daily life, namely physical states (mood, blood oxygen levels), behaviours (food consumption), and
performance. Self-monitoring and self-sensing combine devices equipped with sensors (e.g. EEG, ECG) and computational power. Captured data gets transferred to platforms, in order to analyse and draw value from it. Increasingly, devices are able to absorb data, recognise objects, and respond to information and objects in their environment with greater accuracy. This will increase both the number and complexity of the tasks that they can take on. UK’s NHS predicts that by 2030, sensor technology will be everywhere, making monitoring changes in biological health and behaviour easy and cheap, allowing people to monitor their own health and perform new kind of constant, mobile health checks on themselves. This data can be easily integrated with and enrich existing clinical data.

(i) Embedded devices
Mobility shifts from phones, tablets and wearables to embedded devices. Wearable technology has been accepted and adopted by consumers very quickly over the last years and with Apple entering the market in 2015, this pace will only increase. A key change to mobility we will see in 2015 will be the seamless integration of embedded connectivity into all manner of devices. Whether it is a new car with mobile connectivity built-in or smart home equipment which can be controlled from a mobile, the vast majority of products we buy will be connected by default.

(ii) Wearable devices
Bio-sensing wearables are currently advancing to provide users with a lot of information about their physiological and affective states. The number of wireless sensors and actuators worldwide has exceeded 24 million, presenting an increase of 553% between 2011 and 2016 (Hatler et al., 2012). In 2018, 123 million wearables will be sold, representing a 70% CAGR over the estimated over 20 million in 2014 (BBC, 2013). Wearable technologies are adding new layers to how we collect and share details about ourselves. Wearable technology will be used to help record the world around us, nudge us into action, communicate information between one another, allow us to control our environment, verify who we are and reflect our wellbeing back to us. (PSFK Labs, 2014). Wearable devices will be implemented to monitor and give quick feedback on daily life, especially tied to personal health. (Elon University & Pew Internet Project, 2014)

(iii) Implantable technologies
Bio-connectivity data is expected to redefine healthcare. Thakur (2015) estimates that by 2025, most people in the developed world will have 3 or 4 bio-connectivity medical devices linked to
them on a 24/7 basis. This will include small chips placed under the skin that constantly monitor medical vital signs such as heart rate, blood pressure, temperature, and glucose and oxygenation levels. While in its early stage, and controversial as a method, implantable technology is regarded by many as the future of devices. Technology is becoming part of our bodies, with the resulting data stream being fed into a massive, anonymous healthcare grid that will allow for constant analysis for trends and patterns. This will allow the medical industry to monitor in real time, the outbreak of disease and flu, and predict the emergence of potentially, previously unidentified global or regional health risks. Frost & Sullivan’s Sensor TOE report (2016b) highlights advancements in sensors for healthcare, including skin-based sensors for heart monitoring, ultra-sensitive graphene-infused polysilicone strain and pressure sensors, sensor suits to monitor stroke victims, and smart textiles.

(iv) Ingestible technologies
Frost & Sullivan’s (2016a) report on emerging innovations in the area of smart pills and ingestible sensors lists endoscopic imaging, real-time sensing, targeted drug delivery, and surgery as the key applications and areas of growth. For example, Proteus Digital Health (http://www.proteus.com) aims to transform healthcare by combining three key trends in digital technology – miniaturisation, cloud–based data sharing and mobile. Proteus is contributing to the digital revolution in healthcare through ingestible and wearable sensing. The need for low power, smaller, lighter sensors with enhanced performance attributes and minimal false alarms is driving innovations in the sensors space.

2.1.8 Re-imagining communication via social platforms
The power of social media is exponential, with social media also contributing to the rising datafication trend. Besides contributing new data evidence digital platforms also play a role in helping social movements to effectively influence policy and research (NESTA, 2016). Platforms such as Patients Know Best and Patients Like Me (both developed by people with experience of rare diseases) are already used to share knowledge, and to improve care, by connecting consultants and GPs where official systems have been painfully slow or prone to failure.

2.2 Expectations and considerations

2.2.1 Expectations from big data
The biggest trend identified is data: new data created in novel ways and processed and analysed by applying new increasingly intelligent methods. Increased value is expected from advances in data availability and computational procedures for mining insights and inferences from large data sets. However, harvesting more data cannot automatically generate more value. There are many social and political repercussions with regards to how data is created and processed. Big data comes with high expectations, which have already materialised in many industries. Data and analytics represent a core capability for digital business (Gartner, 2016a). The effective analysis of information is regarded as a level for improved decisions and performance optimisation. Nonetheless, generating value from existing user, operational and service data is a challenging task, which becomes even more complex with the increase in amount of data produced from sensors, devices, interactions and transactions (Internet of Things, mobile and wearable devices, websites and social networks) producing increasing amounts of structured and unstructured data. 

Big data is often said to be characterised by 3Vs: the volume of data, the variety of types of data and the velocity at which it is processed, all of which combine to make big data very difficult to manage. The challenge for organisations is to develop the ability to analyse and order this data and to extract exactly the right information at the right time. The increase in amount of data produced makes ensuring ongoing data quality is a significant task. Rather than being a fixed attribute, data quality is determined by the perspective through which we look at data. Risks associated with big data include: ingestion of useless data (i.e. ingestion of data that do not fit the purpose), ingestion of data from sources of unknown quality, or without authorisation etc. Furthermore, a report published by the Executive Office of the US President (2016) raises the question of the objectivity of big data: while it is often assumed that big data techniques are unbiased because of the scale of the data and because the techniques are implemented through algorithmic systems. Promoting fairness and overcoming the discriminatory effects of data is faced with challenges that relate to the data that are used as inputs to an algorithm to the inner workings of the algorithm itself. In order to harness the potential of big data, organisations need to rethink their current approaches for deploying and managing analytics (Ronanki et al., 2016) beyond the typical approach: Identify what you want to know. Build a data model. Put the data into a data warehouse. Cleanse, normalise, and then, finally, analyse the data. Instead, organisations need to explore what they may be able to do with what is available in terms of data evidence (structured and unstructured data, reliable and less
reliable data) and apply **purpose-driven data analytics** methods (Mayhew et al., 2016). In this context the data lake metaphor model has emerged, according to which all data is stored in a single repository in their native format. Another important issue to be considered is that of data reliability. Organisations should determine how best to stratify the varying trust of the different sources of evidence.

### 2.2.2 Expectations from cognitive technologies

While there is a broad range of problems for which cognitive technologies can provide at least part of a solution, they have limits (Schatsky et al., 2015). The first step in assessing opportunities for cognitive technologies is to understand which applications are viable, acknowledging the imperfection of cognitive reasoning. People are imperfect and AI-enabled services need to be cleverly crafted to both receive emotional input and respond in an emotionally intelligent way. (Fjord, 2016)

### 2.2.3 Expectations from connectivity and new monitoring technologies

The most profound effect of all the ways in which the IoT changes our lives is that it will completely blur the concept of privacy. Sensors and networked monitoring technologies bring with them new ethical implications. Emerging technologies like sensing devices and the IoT are pervasive in a way that nothing else has been, with everyday activities being monitored and people constantly generating informational outputs. Internet Privacy and the risk of unauthorised surveillance, commodification or misuse of personal data etc. raise substantial concerns about privacy and data governance (Mell, 2012; Mantelero et al., 2014, Accenture, 2016a, 2016b). Personal data needs to be controlled, managed, exchanged and accounted. It’s important that privacy practices keep pace with device and service innovation. Initially, deploying Privacy-Enhancing Technologies (PETs) was seen as the solution (e.g. creation of alternative systems that do not collect, share or monetise user data). However, the future of privacy cannot be assured solely by compliance with regulatory frameworks. Currently, the concept of Privacy by Design is proposed which relies on the design and implementation of procedures and systems in accordance with privacy and data protection, already at the planning stage. Privacy assurance must ideally become an organisation’s default mode of operation (Stevenson et al., 2016). For sectors like healthcare and government, cybersecurity is not just a challenge, but a big obstacle to long-awaited digital transformation (Eggers, 2016). In particular, big data poses risks to privacy.
due to (1) the scale, variety and detail of the data collection involved (including tracking and profiling); (2) the challenge of ensuring security measures keep up with the increased volumes of data; (3) the need for transparency when repurposing the data collection for different purposes; (4) the challenges that scale, variety and detail of data pose for data accuracy; (5) the possible use of data to discriminate; (6) the increased economic imbalance between corporations and consumers; and (7) the increased possibilities of government surveillance.

Maintaining confidence in the integrity, confidentiality, transparency and security of the entire system is imperative. Even if not realised, perceived risks to privacy and security could undermine the users’ confidence necessary for the technologies to meet their full potential, and may result in less widespread adoption. Data protection and cybersecurity can’t just be focused on compliance and executed using regular controls. Instead, organisations need to transition to a secure-by-design model, coupling security provisions with cohesive monitoring of potential threats and improving the operational plans by incorporating lessons learned.

3. Digital health ecosystem

More than mere innovations, the emerging technologies of today are having a disruptive effect on everything, changing business, operations and disrupting behaviours. Healthcare is also becoming more and more dependent on medical technologies (medtech) and big data. A recent Nesta report (Bland, 2014) provided an overview of the new wave of medical technologies starting to hit the mainstream, which builds on the re-appropriation of consumer digital technology for healthcare (wearable devices, smartphones etc.). The resulting paradigm shift for healthcare (decentralised, portable personal health) does not solely relate to the way in which patients are healed. In the emerging digital-health landscape, the relationship between doctors, patients, and other stakeholders, and also the way the healthcare system is structured, is changing heavily due to the powerful advances in digital technology (Hartford, 2014; Infosys, 2015). Quoted in the Nesta report (Bland, 2014) is Alice Rathjen’s vision for the Future Web, past the current trend towards mobile access and networks of sensors (IoT), as a “network of digital human beings”, where individuals hold their own portable personal health records, including traditional health records, as well as genetic, physiological and lifestyle data (“a .bio domain owned by each individual”).
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The emerging landscape is characterised by the digitisation of health information (e.g. NHS Digitisation Initiative) and the proliferation of data (Groves et al., 2013), the maturing of EHR (Kuperman, 2013; Peters & Khan, 2014; Mandl & Kohane, 2016), Internet of Things applications (Cousin et al., 2015) and well integrated health information technology (IT) systems (Watson, 2016; Rodriguez-Loya & Kawamoto, 2016). As technology trends increasingly make their way into healthcare, the field witnesses an explosive growth in health data from other sources. The proliferation of digital health information (the so-called secondary data sources, which include clinical information and claims data, existing medical literature, regulatory reports, social media etc.) is creating large datasets from which new insight can be generated (e.g. with regards to medicines therapies).

According to Chandola et al. (2013) healthcare data can be broadly categorised into four groups with regards to their provenance: clinical data, patient behaviour data, pharmaceutical research data and health insurance data. In the light of increasing digitisation, patient behaviour data offer new opportunities. Nonetheless, with privacy concerns are heightened, patient behaviour data can only be leveraged when the owners (doctors, hospitals, and individuals) agree to share it and make it available for analysis.

As cloud computing makes its way into eHealth (Hu & Bai, 2014) moving infrastructures to the cloud, access to data is becoming ubiquitous and new opportunities to improve health care services emerge. Data collection possibilities are also enhanced. Mobile health (i.e. the use of mobile technologies for health research and healthcare delivery) is growing (Research2guidance, 2013) with mHealth apps rapidly developing from basic well-being and lifestyle applications to more sophisticated diagnostic tools. The success of mobile health apps can be explained by two key factors: the high availability of mobile phones and the fact that their technical functionality is particularly well suited for healthcare use. The development of wearable sensors for health monitoring systems is on a growing path (Banaee et al., 2013). Current progress in wearable and implanted health monitoring technologies has strong potential to alter the future of healthcare services by enabling ubiquitous monitoring of patients. A typical health monitoring system consists of a network of wearable or implanted sensors that constantly monitor physiological parameters, which are subsequently relayed using existing wireless communication protocols to a base station for additional processing (Ghamari et al, 2016). The generation of consumer technologies include from advanced sensor-equipped wearables (sensing bio-signals from
heartbeat rates to haptic skin response) to edible IoT technology, “smart” pills that can help monitor both medication regimens and health issues (Korenda et al., 2016), namely, blood sampling sensors, external sensors that connect to the body, epidermal sensors, ingestible sensors and embedded in clothing wearables. Wireless sensor network technologies enable pervasive healthcare systems that provide rich contextual information and alerting mechanisms against odd conditions with continuous monitoring (Özgür & Ersoy, 2010; Triantafyllidis et al., 2015). Analysts project the global IoT-based health care market to grow by 38 percent from 2015 to 2020 (Korenda et al., 2016).

The explosive growth of mobile devices and sensing technologies, the proliferation of online sharing platforms, and the widespread availability of Internet access are producing a rich, new data set that has the potential to revolutionise the way we understand human health and wellbeing and lead to more sophisticated methods and tools for prevention, diagnosis and treatment. The exploitation of big data for the purposes of public health has given rise to a new type of epidemiology. Digital epidemiology or Digital Disease Detection (DDD), harnesses digital data sources to provide local and timely information about disease and health dynamics in populations around the world, in order to accelerate and improve disease outbreak detection and management (Salathé et al., 2012; Vayena, et al., 2015). In this context, patients take a central role in healthcare: visions of a people-powered, knowledge-powered health system, and of patient-led research that leverages patient reported outcomes, are being increasingly promoted. NHS’s vision for 2030 (Blant et al., 2015) sees people managing their own health information, personalising their care and creating new kinds of health knowledge. The trend towards patient engagement included more people managing or in control of their health: people looking after themselves and others, managing a specific health condition or keeping themselves healthy. Patient groups and communities are becoming a new kind of intermediary in the healthcare system. Niche social networking sites dedicated to healthcare professionals and consumers (e.g. PatientsLikeMe), represent important channels for individuals seeking healthcare information, patients wanting to find others who are battling the same health issues, and healthcare professionals connecting to share information, network and learn from each other. In this context, social media and social networking platforms assume an important role, as sources of information about patient experience that has long been missing from research.
A focal point for healthcare organisations will be **healthcare data analytics** and the ability to transform large amounts of data into meaningful information that can be utilised to improve patient care and operational performance. At the core of a data-driven healthcare organisation is the ability to analyse a wide range of big data, from within and outside its four walls (IBM, 2013). This also implies that new information has to be managed and used differently. The digitisation of healthcare is now being exploited and augmented with technologies like mobile, social, cloud computing and analytics (IBM, 2016). Computational methods (computational health informatics) are advancing, in order to tap into the growing availability and accessibility of digital health data (Fang et al, 2016). Healthcare organisation apply clinical and advanced analytics to new and diverse data sources, in order to gain deeper understanding of current or past events, and more accurate insights regarding their performance and effectiveness (retrospective analysis) and to anticipate trends and make estimations (predictive and prescriptive, forward-looking analysis) about patients at-risk (IBM, 2013).

Moving beyond the “digital” trend, IBM (2016) predicts that the future of health is **cognitive**: through the use of cognitive platforms designed to ingest vast quantities of structured and unstructured information from various sources and to allow researchers to find correlations and connections, in order to identify new patterns and insights to accelerate discoveries, treatments and insight. IBM’s Watson Health initiative is aimed at bringing cognitive capabilities to the industry IBM (2015).

An important trend is **cross-continuum data analysis** through the use of healthcare analytics which facilitate a transition from episodic management to the more holistic, health care continuum-oriented population management. Gartner Hype Cycles provide a graphic representation of the maturity and adoption of technologies and applications, and how they are potentially relevant to solving real business problems and exploiting new opportunities. Depicted in Figure 2 is the 2013 Gartner Hype Cycle for Healthcare Provider Applications, Analytics and Systems.
Big data is expected to become the dominant scientific paradigm, (Mayer-Schönberger & Cukier, 2013). Challenges are not solely technical, since the sharing and use of public health data is also conditioned by motivational, economic, political, legal and ethical barriers (Panhuis et al, 2014). Privacy and data protection remain one of the principle concerns and have become much more difficult to protect, especially with old strategies. The new wave of medical technologies pose a particularly difficult regulatory problem: on the one hand they represent an immediate public concern, on the other the speed of digital technology innovation often outpaces regulators.

4. What drives innovation in pharmacovigilance?

The safety monitoring of drugs already on the market represents an increasing concern for the sector. Traditionally, pharmacovigilance has been protected from disruption by strong regulatory oversight and the industry’s risk-averse culture. Currently, the increased supply of information combined with the growing knowledge elicitation capabilities of key technology trends present pharmacovigilance with enormous opportunities. At the same time, new drug safety regulations that require PV teams to cover the full product life cycle. Safety monitoring is gradually expanding its evidence base, moving beyond traditional approaches (i.e. monitoring and statistical analysis of databases of spontaneously reported suspected adverse reactions) towards sophisticated methods that can identify possible safety signals from multiple information
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sources, both structured and unstructured (Franzen, 2017, Edwards & Bencheikh, 2016b). The way forward is the facilitation of knowledge exchange infrastructures that integrate various types of medical data and information (e.g. medicines information, medical data, demographical data, epidemiological data, biomedical data, clinical trial results, etc.) to improve work patterns, processes, and efficiencies across the safety monitoring value chain. The proliferation of secondary data sources coupled with advances in signal detection technologies are reducing significantly the monitoring and reporting cycles for adverse events. The need to bridge the diverse “islands” of information to establish an integrated knowledge base of drugs and health outcomes of interest is imperative (Boyce et al., 2014).

Other major trends that are reshaping the world of pharmacovigilance include the emergence of digital health, the proliferation of social media, the call for proactive surveillance (proactive pharmacovigilance), the intensification of global regulatory expectations, the emergence of personalised medicine & biosimilars.

The role public health informatics infrastructures can play to improve the safety, quality, and efficiency of healthcare are widely recognised (U.S. Institute of Medicine, 2001). Surveillance systems are put in place to facilitate the identification, management and control of public health hazards, including adverse drug effects, etc. that pose a threat to the public's health. Such systems bring together health and information technologies to support the systematic collection and processing of relevant health surveillance data and facilitate evidence-based public health decisions.

Surveillance is a key function of public health. The U.S. Centers for Disease Control and Prevention (2012) define Public Health Surveillance as “the ongoing, systematic collection, analysis, and interpretation of data essential to the planning, implementation, and evaluation of public health practice”. Surveillance is undertaken to inform disease prevention and control measures. Its primary goal is to provide an early warning system so as to identify public health emergencies and to subsequently guide public health policy and strategies. It is therefore closely integrated with the timely dissemination of these data to those responsible for prevention and control. An effective surveillance system features the collection and consolidation of relevant data from various sources for the detection of health events (including the investigation and confirmation of particular cases or outbreaks) and reporting mechanisms for the notification of health policy authorities.
In the field of pharmacovigilance, there is a growing interest in innovative methods for real world evidence generation from real world data in relation to medicinal products. Real world data can be described as observational data that is not collected under experimental conditions (randomised clinical trials) but data generated in routine care from information related to a patient's treatment. It can come from patient registries, electronic health records, insurance data and web/social media (STAMP Commission, 2016).

Real-world data is starting to be used in the post-authorisation phase to complement spontaneous reporting systems, e.g. by measuring the background incidence of adverse events so that suspected adverse reactions reported can be put into perspective (observed vs. expected). There is great potential to extend such approaches to study the use of medicines more systematically, to investigate their efficacy in real-world use and to rapidly and iteratively monitor (rapid-cycle evaluation) the use, safety and efficacy of new medicines.

Big data is becoming an increasingly critical component for monitoring drug safety and effectiveness (CIOMS, 2013; Tuccori & Wallberg, 2017). Big data comprises much larger volumes, wider varieties and greater velocities of data from traditional sources such as electronic medical records and from nontraditional sources such as social media and public health records. Online physician communities, electronic medical records, and consumer-generated media are also potential sources of early signals regarding safety issues and can provide data on the reach and reputation of different medicines and help highlight rare or ambiguous safety signals with greater accuracy and speed (Cattell et al., 2013). Instead of addressing each knowledge source individually, a holistic approach is needed as different data sources (individual case safety reports, observational data, clinical trials and meta-analyses) used in pharmacovigilance have unique characteristics that complement each other for the overall benefit–risk evaluation of medicines (Arlett & Kurz, 2011).

For pharmacovigilance this represents an era of “Digital Darwinism” similar to the one experienced by businesses (Schwartz, 1999; Solis, 2011; Kreutzer & Land, 2014). Society and technology are evolving at a rapid pace, introducing new directions and challenging how the sector adapts in order to draw benefit. Pharmacovigilance is experiencing a paradigm shift, and is faced with challenges that can broadly be described in two dimensions: on the one hand pharmacovigilance systems are extending their scope from a systematic and health organisation-driven perspective towards the inclusion of the “consumer” input, while at the same time the
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technological and methodological means employed are evolving from established sector-specific approaches towards the assimilation of technical innovations imported from other sectors (Figure 3). Tapping into emerging technologies can lead to process improvements. As technology creates new capabilities for research moving from analogue to digital processes, methods need to combine ideas from information systems and data science with health and medical science to harness their full potential and achieve results that no one could produce individually.

![Diagram showing drivers of pharmacovigilance innovation]

**Figure 3. Drivers of pharmacovigilance innovation**

Increased patient engagement during the post licensure stage can significantly improve drug lifecycle management. As a result pharmaceutical companies get assurance that their product is administered and delivered as intended, in a way that can optimise efficacy and outcomes (adherence program) and have improved patient outcome and experience monitoring, social listening (Lush et al., 2016).

Digital services have enabled consumer–driven innovation and customisation in other sectors and is also gradually entering healthcare (Bland, 2014). Consumer–driven innovation is happening in pharmacovigilance as well. A key element for realising the full potential of pharmacovigilance is the concept of **end user-centricity** (Xu, 2016) and the adoption of a holistic approach that recognises that end users (patients) are vital and independent stakeholders in the co-creation and value exchange of services and experiences (Smith, & Benattia, 2016). Only the effective exploration of the “consumer” perspective (through the affordances of big data, social media etc.), can add significant value to pharmacovigilance. For this purpose, new
technological directions need to be investigated, since the requirements exceed the capabilities of the established methods. The domain needs to harness progress in the area of physical-cyber and cyber-social systems. However, this needs to be pursued in a contextually-aware fashion, taking into consideration and satisfying the complex conditions of the extended safety monitoring ecosystem.

End user-centricity represents a transformational opportunity for pharmacovigilance. In this context, the traditional roles and operational models of both regulatory institutions and pharmaceutical companies are changing (Moa, 2016). Their working methods are increasingly driven by knowledge (Champagne et al. 2015a, Pappa et al. 2009). The growing volume and detail of information captured, coupled with new machine-learning and deep-learning capabilities, and breakthroughs in natural-language processing could have an extended impact on productivity and effectiveness. Advanced analytics, sensors, and the automation of complex decisions are capable of delivering a step change in the efficiency, speed, quality, and responsiveness of business processes (Champagne, et al. 2015b). Medicines stakeholders have the possibility to link and analyse data from clinical care, laboratories, sensors, apps, social media, insurance claims, etc., in order to generate real-world evidence about a drug’s efficacy. As information constantly flows in from different sources, and with every generation of tools unleashing even bigger opportunities and changes, organisations have the opportunity to use these capabilities not only to improve their core operations, but also to widen the scope of pharmacovigilance beyond signal detection, to shed light on other aspects of drug safety information that can help improve the management and treatment of ADRs and directly serve the health of the public. For example, harnessing information that characterises the use of medicines in everyday practice and people’s attitude and behaviour towards ADRs, can be of use to healthcare professionals for optimising treatment (Pitts et al., 2016; van Puijenbroek & Harmark, 2017). In this light, the safety monitoring of pharmaceuticals in the market assumes a strategic role across the entire business value-chain, which in turn creates new expectations for advanced knowledge and more sophisticated data-driven insights from the field. This also implies a shift from population- and regulation-based pharmacovigilance to patient-centred pharmacovigilance (van Puijenbroek & Harmark, 2017). In this sense, pharmacovigilance could be described as being in a state of kaizen (Imai, 1986), characterised by continual expansion of scope and continuous improvement, balancing the need to capture value from deep and up-to-real-time
information with the affordances of technological innovations. Capturing value from digital is not just about the establishment or improvement of a fixed set of insight generation processes, but rather about the ability to continuously establish new investigation environments for the extraction of more sophisticated and targeted insights. Rapidly developing innovations in biomedical informatics have made significant contributions to the infrastructural development of pharmacovigilance, while posing a challenge to safety monitoring in finding ways to include new sources of safety information (Beninger & Ibara, 2016).

The traditionally reactive pharmacovigilance systems are gradually transforming and expanding into proactive, holistic benefit-risk management systems in order to accommodate the growing need for immediate and reliable drug safety information. Moving forward, pharmaceutical and biotechnology companies must not only monitor for adverse events, but also proactively assess and manage drug risk throughout a product’s lifecycle. Developing a pharmacovigilance risk management plan with a risk minimisation action plan (RiskMAP) for high risk products is becoming ever more essential. The pharmaceutical industry has already been processing huge volumes of data, mainly for the purposes of research and development, sales and marketing and medicine distribution in the marketplace. Currently, they are faced with a new mission: Pharmaceutical companies who have previously focused on "selling the pill" now find themselves faced with the question how to develop truly integrated patient care "beyond the pill."

As a result pharmaceutical companies increasingly need to look into available big data from multiple sources, also from the perspective and for the purposes of drug safety. This will allow pharmaceutical companies to proactively respond to the issues that could impact business.

Technologies and devices are also growing in importance. Wearables data are already making their way into drug development as a means to improve the efficiency of Phase I and II drug trials, providing researchers with meaningful trial participant insights that go beyond the traditional questionnaire or interview-based methods (Comstock, 2016; Plumer, 2016). The World Economic Forum (2015b) predicts that leveraging the Internet of Things in healthcare (Industrial Internet) will allow connecting measurements to treatments and enabling smart drug delivery systems to react to patient conditions faster and more reliably, improving patient safety and experiences. It will also provide more accurate information on drug consumption. On the basis of the analysis above, it can be concluded that the emerging paradigm for pharmacovigilance has the following attributes:
Table 9. Attributes of the emerging paradigm for pharmacovigilance

- Electronic Pharmacovigilance: digitisation of pharmacovigilance processes, interconnection of local and national spontaneous adverse event reporting systems and infrastructures, harmonisation of legislation and methods;
- Proactive pharmacovigilance, exploiting diverse information channels for real-time signal detection. Collection of case safety information as a continuous pre-organised process;
- Active surveillance to address priority safety concerns (e.g. follow-up of defined patient cohorts);
- Easy and rapid access to all sources of pertinent safety data;
- Innovative workflows and deployment of relevant automation in performing pharmacovigilance activities;
- Pharmacovigilance organisations transforming their operations and engaging in external collaborations and business partnerships;
- There are numerous patient monitoring devices and applications that continuously monitor physical/physiological parameters of a person, creating data that can be of service to pharmacovigilance;
- More information is available about post licensing drug performance;
- Patients becoming increasingly active in sharing their experiences through online social communities;
- Fuller engagement of stakeholders: Omni-channel conversations with physicians and patients, feedback channels;
- Need for increased transparency and trust, intensified regulatory expectations.

In this context, and as pharmacovigilance is gradually acknowledging the usefulness of secondary data sources, research in information technologies is expected to contribute new advanced algorithms for the detection of signals from different sources, moving the sector beyond the typical disproportionality analysis of spontaneous reports (Lichtenfeld, 2016). Natural language processing and machine learning will allow for increased sense making from complex and unstructured information streams.

5. Generic technologies: Trends and forecasts in pharmacovigilance

In recent decades we have seen accelerated development within each layer of physical, cyber, and social domains that have a strong bearing on human experience. Exponential technology is disrupting the various stages of the pharmacovigilance information value-chain. According to the analysis above, key drivers include: Data sourcing (Storage, Cloud, Datafication, Big Data, new data streams, Social Media, intelligent interfaces, sensors, Connectedness, consumerisation, patient empowerment); Data aggregation (Advanced networks, Bandwidth, Internet of Things, Cloud-based workflows); and Data processing (Processing power, Artificial Intelligence, real-
time data processing and analysis). Technology trends impacting the entire value chain can be summarised as follows:

**Table 10. Technology trends impacting the pharmacovigilance value chain**

- Big Data (new technologies and data storage solutions)
- Cloud-based workflows
- Smart devices and wearable computing that allow people to measure, monitor and datafy activities in their daily lives.
- Internet of Things
- Constant connectedness
- Multi-channel technologies using business intelligence systems to get user's information
- Cross-platform interoperability
- Artificial Intelligence (AI) building machines that can simulate human intelligence.
- Ambient Intelligence, making the surroundings of humans an intelligent space.
- Human Computer Interaction (HCI), building seamless interfaces between humans and machines

Innovation initiatives in drug safety monitoring need to ensure that emerging problems are promptly recognised and efficiently addressed. At the same time innovation has to find solutions for old problems. During the past decade, the pharmacovigilance environment has made considerable progress. However, still today innovation efforts are hindered by expensive and outdated systems, limited integration of data, inconsistent standards, unpredictable and highly variable processes, and complex, non-harmonised global regulations. Today, the industry finds itself in the very early stages of a long-term journey toward a more data-driven and analytic-enabled approach to post-marketing surveillance and drug safety management as a whole. Despite advances in methods, expectations are high and there is lingering skepticism regarding the utilisation of secondary data, with some considering secondary data inferior to the primary research data. For example the general consensus is that MedWatch captures around 10 percent of adverse events, which is considered very low. Signal to noise ratio issues associated with social media are also a challenge. Unlocking the full potential and making the shift from volume to value, also remains a challenge, since each data source presents unique challenges. Leveraging new technologies will enable pharmacovigilance to develop smart custom-made investigation environments for the early detection and assessment of signals of adverse reactions on the basis of holistic approaches for intelligent information processing and integration. Pharmacovigilance is not anymore about reporting individual cases or aggregate reports. It is about establishing ongoing processes to monitor an always evolving benefit/risk profile, with a well-established safety
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governance model across the enterprise, and a solid underlying process for signal detection and management. The objective is not to simply generate more signals, but to produce timely, reliable, and actionable results, namely to: (a) generate better signals, to allow for effective and efficient safety risk mitigation; and (b) produce and make available relevant information in a relatively short and relevant timeframe (real-time pharmacovigilance), to allow for timely analysis and immediate action to be taken in response. In can be concluded that the milestones of the information value-chain are: (a) tapping into data sources (data access); (b) extracting information (potential signals); (c) extracting knowledge (verified, actionable signals); (c) taking action based on knowledge (recommendations).

Challenges to realising the full potential for real world evidence include: incomplete access to electronic healthcare data from different countries and a lack of hospital in-patient data; variable data quality and a lack of harmonisation; the need to develop methods for efficacy and HTA outcomes; and delays to start studies. (STAMP Commission, 2016). Salathé (2016) stresses that data from traditional health systems and patient-generated data have complementary strengths (high veracity in the data from traditional sources and high velocity and variety in patient-generated data) and, when combined, can lead to more-robust public health systems. However, they also present unique challenges. Patient-generated data, being often completely unstructured and highly context dependent, represent a challenge for machine-learning. While technical challenges can be solved, the problem of verification remains, and unless traditional and digital epidemiologic approaches are combined, these data sources will be constrained by their intrinsic limits.

Realising the full potential of technology implies not only a profound transformation in the way providers interact with consumers, but also the reinvention of their internal processes and organisation and the development of new partnerships among stakeholders. A joined-up approach can help improve the quality of health data, information, and knowledge used to support decisions at all levels and in all domains of the health sector. Leveraging new technologies will enable pharmacovigilance to develop smart custom-made investigation environments for the early detection and assessment of signals of adverse reactions on the basis of holistic approaches for intelligent information processing and integration. However, changing the activity from a traditional approach to one based on knowledge organisation comes with several challenges, making it imperative to elaborate a detailed methodology for the procedure. Key questions include:
Table 11. Challenges to pharmacovigilance innovation

- How can we develop strategies and long-range plans that maximise success across disparate sources of evidence and within an extended community of stakeholders?
- How can we ensure quality and timeliness?
- How can we ensure effectiveness and efficiency?
- How can we reduce uncertainty and manage risk?
- How can we identify emerging opportunities and threats?

Reporting on the outcomes of the 2016 Pharmacovigilance Days (PHV Day 2016), a series of meetings that bring together safety experts from the pharmaceutical and healthcare industry to discuss the relevance of drug safety and pharmacovigilance, Xu (2016) highlighted the use of digital media for directly engaging with patients as one of the critical questions in pharmacovigilance. Pharmacovigilance is currently expanding its evidence base. In the following sections we examine current efforts in Electronic health records (EHR) and social media. The use of electronic health data in pharmacovigilance is growing. EHR contain patient information such as demographics, medications, laboratory test results, diagnosis codes and procedures and can provide a new platform to improve and complement drug safety surveillance strategies. There is growing interest by safety stakeholders in exploring the use of social media for the purposes of pharmacovigilance. Health information posted online by patients represents an untapped source of post marketing safety data.

6. Emerging sources of evidence

6.1 Electronic Health Records (EHRs)

ISO describes Electronic Health Records (EHR) as an overall term for “a repository of information regarding the health status of a subject of care, in computer processable form”. It refers to the systematised collection of patient and population electronically-stored health information in a digital format. An EHR is a record of a patient's medical details, including history, physical examination, investigations and treatment. The advantage is that an EHR is a longitudinal electronic record of patient health information generated by one or more encounters in any care delivery setting. EHRs document patients' state of health over time and also the therapeutic interventions to which these patients were subjected and their outcomes. Furthermore, with EHR typically being part of an integrated health information system (IHIS) their great value lies in the fact that it allows a distributed collection of clinical data as part of the
overall workflow. For this reason the use of already available EHR data for research is having a marked impact on pharmacoepidemiology (Liu et al., 2013; Harpaz et al., 2013, MIT Critical Data, 2016).

EHRs are characterised by diversity, in terms of information stored, the standards employed and the format. EHR data may be available in structured (databases), semi-structured (ow sheets) and unstructured formats (clinical notes). While much still needs to be done to create standardised methods for sharing and making sense of anonymised EHR (Meystre et al., 2010) it is now possible to link different data sources, which allows complex research questions to be addressed (Trifirò, et al., 2009). For example, the analysis of comprehensive EHR patient data collected in real time during doctor or hospital visits provides an opportunity to better understand diseases, treatment patterns, and clinical outcomes in an uncontrolled, real-world setting. Harmonisation is required for the identification of events and information of use to medicinal safety investigations (Pappa et al., 2006). The inherent complexity of EHR may affect the effectiveness of pharmacovigilance insight. Hospitals represent a complex organisational setting having multiple objectives and complicated and highly varied structures and processes (Boonstra & Govers, 2009). As a result the implementation and management of hospital-wide EHR systems is a complex exercise conditioned by a range of organisational and operational/technical factors.

Mining clinical data is a fast-evolving field (Wang et al., 2010; Jensen et al., 2012; Yadav et al. 2015). The growing digitalisation in routine medical care has led to an enormous increase in clinical data. EHR storing patient information such as demographics, medications, laboratory test results, diagnosis codes and procedures, provide a new platform to improve and complement drug safety surveillance strategies, despite lacking agreement on interoperability standards and schemes for privacy and consent. EHRs contain both structured and unstructured information. The former includes demographic information (e.g. birth date, race, ethnicity), encounters (e.g. admission and discharge data), diagnosis codes (historic and current), procedure codes, laboratory results, medications, allergies, social information (e.g. tobacco usage) and some vital signs (blood pressure, pulse, weight, height) are all stored in structured tables. The later refers to clinical notes (free text narratives) providing details about medical processes, treatments and outcomes (surgical note) or other information regarding a patient's medical history (diseases as well as interventions), familial history of diseases, environmental exposures and lifestyle etc. Natural language processing (NLP) tools and techniques have been widely used to extract
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knowledge from EHR data (Wang et al., 2009). In dealing with the complexity of EHR use for the purposes of pharmacovigilance, it is helpful to know which factors are seen as important in the literature and to capture the existing knowledge on the subject. This could contribute to greater insight into the underlying patterns and complex relationships involved in EHR-based pharmacovigilance and could identify ways to tackle EHR implementation problems. The last two decades have witnessed the development of key data resources, expertise and methodologies. There have been a number of initiatives aimed at increasing the accessibility and utility of EHRs across multiple Member States for both clinical research (EHR4CR, GetREAL, EMIF, epSOPS) and drug safety (EU-ADR, PROTECT, ADVANCE). Following is a brief presentation of some important initiatives:

In 2008, the EU funded project ‘Exploring and understanding adverse drug reactions by integrative mining of clinical records and biomedical knowledge’ (EU-ADR) set out to design, develop and validate a computerised system to process data from eight electronic healthcare record (EHR) databases and several biomedical databases for drug safety signal detection. The foundation for EU-ADR’s strategy relies on in-depth semantic data mining of electronic health records (Oliveira et al., 2012). Data extracted from EHR resources are semantically harmonised for data mining, generating a raw drug-event pair list. The signal substantiation process analyses the submitted data, re-ranking the signal list, based on multiple algorithms. Users trigger data analysis and exploration to validate the system operability. Within this project, an event based approach was adopted where a focused set of events of special interest in pharmacovigilance are evaluated for their association with all drugs captured in the EHR databases. Each of the eight databases in EU-ADR has unique characteristics depending on its primary objective and local function (i.e. administrative claims or medical records) and contains medical information coded according to different languages and disease terminologies. For these reasons, queries for data extraction concerning potential adverse events have to be created based on local expertise. Due to structural, syntactic, and semantic heterogeneities of the databases participating in the EU-ADR project, it was not possible to construct a single query for data extraction that could be used as such in all databases identify possible safety signals from a range of sources, including the pharmaceutical R&D process (Trifirò et al., 2011). In the USA, the Food and Drug Administration (FDA) started the Sentinel Initiative (Behrman et al., 211; Robb et al., 2012) in recognition of the need to use innovative methods to monitor FDA-regulated products and to
enhance public health safety by secondary use of anonymised health data. In 2007, Congress passed the FDA Amendments Act (FDAAA), mandating the FDA to establish an active surveillance system for monitoring drugs that uses electronic data from healthcare information holders. The Sentinel initiative is the FDA’s response to that mandate. The aim is to leverage existing healthcare information to enable FDA to conduct active post-market safety surveillance to augment its existing surveillance systems. The initial efforts of FDA have been implemented through the Mini-Sentinel pilot project (Curtis et al., 2012), which is intended to function as a kind of laboratory that can inform FDA on scientific and technical issues related to the development of the Sentinel System. The Observational Medical Outcomes Partnership (OMOP) (Stang et al., 2010) is a public-private partnership designed to help improve the monitoring of drugs for safety. The partnership is developing and testing research methods that are feasible and useful to analyse existing healthcare databases to identify and evaluate safety and benefit issues of drugs already on the market. The European Medical Information Framework (EMIF) project targets the creation of an innovative and connected patient registry catalogue that consistent re-use and exploitation of currently available patient-level data (Roberto et al., 2016). The PROTECT project funded by the EC and the European Federation of Pharmaceutical Industries and Associations (EFPIA) under the Innovative Medicines Initiative (IMI) aims to strengthen the monitoring of benefit-risk of medicines in Europe by developing innovative methods that will enhance the early detection and assessment of adverse drug reactions from different data sources and enable the integration and presentation of data on benefits and risks. A methodological framework for pharmacoepidemiological studies was developed and tested to allow data mining, signal detection and evaluation in different types of datasets, including spontaneous reports, registries and other electronic databases.

The use of EHR databases requires an understanding of how healthcare data are generated from the initial patient encounter all the way to completion of the database entry. However, several differences in the way patient data is recorded exist, conditioning the extraction of events across databases (Avillach et al., 2013). These include differences in the granularity of disease coding system used and the recording practices of data contributors, but also relate to the availability of supplementary clinical information, to linkages with information containing laboratory findings or procedures, availability of follow-up information on events that occur afterwards, outside primary care practice or hospitalisation etc.
A broad range of ethical, legal and technical limitations may hinder the systematic exploitation of EHR data. Despite their great potential, EHR mining is faced with technical challenges that relate to the interoperability and integration of scattered, heterogeneous data, in addition to ethical and legal obstacles that limit access to the data (Kush et al., 2008; Taylor, 2008). Standardisation of EHR contents and agreed standards for interoperability and schemes for privacy and consent are needed (Rezaeibagha et al., 2015; MIT Critical Data, 2016; Hruby et al., 2016).

6.2 Social media & networking data

Patient perspective has always been an essential component of medicines safety monitoring. Postmarketing safety surveillance relies mostly on data from spontaneous adverse event reports, medical literature, and observational databases. Limitations of these data sources include potential underreporting, lack of geographic diversity, potential of patients’ perspectives being filtered through healthcare professionals and regulatory agencies, and time lag between event occurrence and discovery (Powell et al., 2016; Salathé, 2016). With more effort applied to patient-centric drug development, it becomes increasingly important to incorporate the patients’ voice in the pharmacovigilance systems and process. A new health research model has emerged described as “crowdsourced health research studies”, which takes advantage of multiple sources of information, including group interactions in online virtual communities and the internet to advance health research (Lamas et al., 2016). In this context, there is growing interest by safety stakeholders in exploring the use of social media (in the form of ADR reporting via social media channels or “social listening”) to supplement established approaches for pharmacovigilance. Health information posted online by patients is in abundance and is often publicly available, and thus represents an untapped source of postmarketing safety data that could supplement data from existing sources of safety information (Bagheri et al., 2016).

Social Networking Sites (SNSs) and applications allow for the exchange of user-generated content where people talk, share information, participate and network. Boyd & Ellison (2007) describe SNSs as “a web-based service that allow individuals to (a) construct a public or semi-public profile within a bounded system, (b) articulate a list of other users with whom they share a connection, and (c) view and traverse their list of connections and those made by others within the system. The nature and nomenclature of these connections may vary from site to site”.
More and more individuals are making use of SNS to communicate and stay in contact with family and friends, to engage in professional networking or to connect around shared interests and ideas. There currently exists a rich and diverse ecology of SNSs, which vary in terms of their scope and functionality: general purpose and specialised community sites (e.g. Facebook and LinkedIn), media sharing sites (e.g. MySpace, YouTube, and Flickr), weblogs (blogs), micro-blogging sites (e.g. Twitter) and question/answer discussion forums. Social media usage has witnessed a nearly tenfold increase in the past decade: 65% of adults now use social networking sites (Pew Research Center, 2015). Between 2005 and 2011, social network sites experienced remarkable growth in active users, as well as shifts in the popularity of key sites. Facebook and LinkedIn have experienced tremendous growth. Micro-blogging services such as Twitter and Tumblr are also on a growing path. As a result, social media is creating real-world data at an unprecedented rate. People use social media to discuss their everyday lives, including their health and their illnesses. This might be a conversation with friends on Facebook or Twitter, or discussions with other patients on PatientsLikeMe, where they exchange information regarding diagnoses, treatments, coping mechanisms, medications and outcomes.

The term Social data refers to data from social networks. The fact that users publish in SNS a P); (ii) data can be observed or recorded (e.g., through cookies monitoring accesses to a website), with or without consumers’ knowledge, or explicit consent; (iii) data that can be inferred, also by mixing several sources of data that are, by themselves, anonymous. According to the context and purposes of data disclosure, social networking data fall under these categories: service, disclosed, entrusted, incidental, derived or behavioural data (Schneider, 2009; Van Alsenoy, 2014). A distinction can also be made between collected (backoffice) and front-end data. The former refers to data collected by the service provider, while the latter to data that is knowledgeably shared (Public/Disclosed Data, Social Data). The context of disclosure might be a conversation with friends on Facebook or Twitter, or discussions with fellow patients on online social networks like PatientsLikeMe, where they will share diagnoses, treatments, coping mechanisms and outcomes with one another. The enormous number and diversity of conversations that can take place in a social media setting, means that there are format and protocol implications for stakeholders seeking to make sense and extract knowledge from them.

A range of motivations for disclosure in social network sites exist. The motivation to connect and learn about one another has given rise to niche SNS. Recent years have seen the emergence and
proliferation of **SNS dedicated to healthcare communities** of health professionals and/or consumers, which have become particularly popular among patients, as a platform that allows them to exchange information about their health condition with others who are battling the same health issues. Such networks include: PatientsLikeMe (www.patientslikeme.com) a social networking community that enables people to share information that can improve the lives of patients diagnosed with life-changing diseases. Recording the real-world experiences of patients, healthcare professionals etc, these social networking sites are gradually becoming important channels for healthcare information (Nakamura et al., 2012). The potential of online social network data, stemming from the experience of individual patients to support formal clinical trial procedures is gradually being recognised (Frost et al., 2011). Specialised platforms have emerged (e.g., DailyStrength, MedHelp), in which users discuss their health-related experiences, including use of prescription drugs, side effects and treatments. Users tend to share their views with others facing similar problems/results, which makes such social networks unique and robust sources of information about health, drugs and treatments. Due to the popularity of such networks, and the abundance of data available through them, research on public health monitoring, including ADR monitoring, has focused on exploiting data from these sources in recent times. **PatientsLikeMe** (PatientsLikeMe.com) is a social networking community that enables people to share information that can improve the lives of patients diagnosed with life-changing diseases and learn from the real-world experiences of other patients with similar issues. PatientsLikeMe provides support groups and data sharing for patients with various conditions including MS, Parkinson’s disease, HIV, epilepsy and people with transplanted organs. Participants note their daily state of health, including details about their ailments and symptoms. They provide information about medication, the drugs and dosages they receive and score how well they alleviate their symptoms. The site then compiles the information into graphics available for anyone to see. **DailyStrength** (DailyStrength.com) is a comprehensive health network of people sharing advice, treatment experiences and support. It includes over 500 support groups and research about latest drugs, treatments and alternative therapies. **MedHelp** includes a section dedicated to Drugs. For each drug in this section, there is a brief introduction, and MedHelp users are allowed to post their experiences and thoughts or comment on the posts of other users. **Trialreach** is a portal for patients to access information about clinical trials near them. It was born from the founder’s frustration with the fragmentation of clinical trials in the
UK. People could only apply for trials in their own NHS Trust. The platform offers free access to clinical trial information, and is free for public sector trials to advertise. Trialreach sells the service to large pharmaceutical clients looking for patients. SNS data have come to attract the interest of a wide range of actors. SNSs permit a large amount of information from different sources to be collected. Datasets can be continuously monitored in order to identify the emerging trends in the flows of data. This approach is revolutionary and differs from the traditional sampling method, which is based on the extraction of a representative sample from the total statistical population.

6.2.1 Social Media and Digital Health

With a demonstrated use as a source of information (Vance et al., 2009), social media have been used by healthcare stakeholders, in order to distribute information about diseases and their treatment, medicines and announcements (Choudhury et al. 2014). Currently the potential of SNSs as a source of insight is increasingly recognised. Social media mining is becoming an integral part of public health monitoring and surveillance (Paul et al., 2016), assisted by advances in automated data processing, machine learning and natural language processing (NLP). Applications include epidemiological investigations, e.g. mining twitter data for disease topic detection and surveillance (Paul & Dredze, 2011; Byrd et al, 2016), including tracking the spread of infectious diseases. However, the analysis of health social media content requires innovative approaches (Benton et al., 2011).

6.2.2 Social Media and pharmacovigilance

In recent years, many scholars have investigated the availability of adverse event information in social media sources and the necessary technology and methods to extract it. Statistics show that there is value in pharmaceutical companies and regulatory authorities taking a more proactive approach to social media monitoring (Sarker et al.,2015). Proactive monitoring could provide early warning of new adverse events or clinical information that helps guide drug development and avoid preventable litigation. Regulators and pharmaceutical companies are also starting to monitor social media posts for potential ADR signals. Previously much of the interest in social media has been on the marketing front. Nowadays, their potential application for improving drug safety and pharmacovigilance is increasingly recognised, namely for the identification of signals
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of unknown ADRs, unknown drug-drug interactions (DDIs) of concomitant medications, which are often linked to unexpected ADRs (Yang & Yang, 2013).

“The quantity and near-instantaneous nature of social media provides potential opportunities for real-time monitoring of ADRs, greater capture of ADR reports and expedited signal detection if utilised correctly (Sloane et al., 2015). According to Liu & Chen (2015b) an advantage of patient social media is that they cover a large and diverse population and contain millions of unsolicited and uncensored discussions about medications. Furthermore patient reports of adverse events in social media are more sensitive to underlying changes in patients’ functional status than clinical and spontaneous reports. Today, social media form officially part of the potential sources of data of interest to pharmacovigilance. Most of the regulatory guidance and hence pharmacovigilance activities involving social media and internet are primarily focused around screening of social media sites and follow-up of reported safety data.

Pharmacovigilance has mainly relied on voluntary reports by health-care professionals, such as the Adverse Event Reporting System (AERS) used by the US Food and Drug Administration (FDA). However, the reporting rate of such systems is low, which delays the detection of ADRs and increases the possible number of deaths due to ADRs. In addition, patient reports have been shown to be of equal or more importance than the reports of health professionals, especially with the increasing use of social media and social networks (such as Twitter) in which users freely share their personal experiences. By mining the relationships between drugs and ADRs from data reported by online users on health-related issues, we can speed up the process of detecting and confirming ADRs. A related project is to mine social media data for off-label uses of medications. By mining associations between drugs and medical conditions in social media, and comparing the reported medical conditions with the ones officially approved for the drugs, we can discover new uses for these drugs, if such new associations were reported as being positive (i.e., the drug helped to cure the medical condition). These newly discovered associations can then be confirmed by clinical trials for market approval.

Increasingly, new treatments for rare diseases are becoming available, and many of them may be tested only on small patient groups. Therefore, continuous monitoring of the benefits and risks that patients experience becomes critical. While mining “big data” to detect suspected ADRs is being explored in pharmacovigilance generally, this method may have limited application to orphan drugs (Price, 2016). In the context of pharmacovigilance, social media can be utilised in
various ways for the collection of information directly from patients in a solicited (formal reporting channel): or unsolicited manner (social media monitoring). For example, the WEB_RADAR project is investigating the use of mobile applications and social media for pharmacovigilance reporting. Algorithm sensitivity is quite high, while difficulties exist in the identification and processing of data (unstructured data). Monitoring social media for adverse event reporting involves several challenging steps: Data harvesting (collection of raw data); Translation (standardisation of drug names and vernacular symptom/event descriptions); Filtering (identification of relevant informative posts and data cleaning); De-identification (removal of personally identifying information); and Supplementation (addition of other data sources to facilitate the review process and contextualise the results and assist interpretation).

While the evidence of social media’s ability to enhance pharmacovigilance methods and processes continues to grow, many challenges remain. One of the principal challenges is the extraction of medical entities from noisy patient-generated content. Efforts towards the automatic text classification for ADR detection are receiving growing attention (Chee et al., 2011; Sarker & Gonzalez, 2015; Yang et al., 2015; Zhang et al., 2016). However, lexicon-based approaches (Leaman et al., 2010) for medical entity recognition and tools like the MetaMap (Aronson, 2001), developed by the US National Library of Medicine to identify medical concepts into the concept codes from the Unified Medical Language System Metathesaurus (UMLS), are not sufficient, given the informal, colloquial nature of discussions and the non-adherence to standardised terminology used by participants. User-expressed medical concepts are often nontechnical, descriptive, and challenging to extract. Human curation is also investigated for the purpose of establishing a gold standard by which future, automated classification methods may eventually be compared (Casperson et al, 2016). The framework proposed by Liu & Chen (2015a) employs a hybrid approach combining statistical machine learning methods and rule-based filtering. Advanced machine learning-based NLP techniques are also promoted by Nikfarjam et al. (2015).

User comments to health-related social networks contain extractable information relevant to pharmacovigilance. Research efforts demonstrate that it is possible to extract complex medical concepts, with relatively high performance, from informal, user-generated content. Another source of user-generated content on the Internet are health-related social networks and forums. Recognising this potential the FDA has engaged PatientsLikeMe in a research partnership to
generate more AE data. According to PatientsLikeMe, it has collected more than 110,000 adverse event reports on 1,000 different medications, data that the FDA will now be able to access and analyse in addition to its existing sources of information (Comstock, 2015a). Together with Google, FDA examined the potential use of search to identify adverse drug reactions (Comstock, 2015b). Leaman et al. (2010) developed an automated system to identify adverse reactions by means of a primary lexical method, which was applied to mine data from the website DailyStrength, with satisfactory results. Social media have the potential to become an added new-age tool to monitor data in real-time, making it an early indicator of potential safety issues for further investigation.

6.2.3 Micro-blogging (Twitter)

The noisiness of Twitter data (short sentences, fragmented sentences, use of abbreviations, misspelling errors) can significantly impact the performance of classification methods (Bian et al., 2012). Twitter could potentially be a lucrative source of otherwise unreported adverse drug events, but that the data is noisy and hard to process (Bian et al. 2012; O’Connor et al., 2014, Carbonell et al., 2015). Freifeld et al. (2014) concluded that while patients reporting AEs on Twitter showed a range of sophistication when describing their experience, the wholesale import of individual social media posts into post-marketing safety databases would not be advisable. Rather, in parallel with other post-marketing sources, these data should be considered for idea generation, and reasonable hypotheses followed up with formal epidemiologic studies. Additional work is needed to improve data acquisition and automation. Sarker et al. (2015) identified studies describing approaches for ADR detection from social media from the Medline, Embase, Scopus and Web of Science databases, and the Google Scholar search engine. Their review suggests that interest in the utilisation of the vast amounts of available social media data for ADR monitoring is increasing. In terms of sources, both health-related and general social media data have been used for ADR detection—while health-related sources tend to contain higher proportions of relevant data, the volume of data from general social media websites is significantly higher. There is still very limited amount of annotated data publicly available, and, as indicated by the promising results obtained by recent supervised learning approaches, there is a strong need to make such data available to the research community. According to Sloane et al. (2015) several technical challenges to signal extraction from SNSs exist with regards to
terminology, use of colloquial language, ambiguity etc., with the principal related to the named entity recognition (NER) problem, i.e. the fact that both drug names and reaction terms can be described in a variety of ways.

6.2.4 Search log data

Several scholars have demonstrated how search logs can be used for the early identification of adverse drug reactions. White et al. (2013) demonstrated that anonymised signals on drug interactions can be mined from search logs, using the example of a 2011-reported adverse event (hyperglycemia) due to a previously unknown interaction between the drugs paroxetine, an antidepressant, and pravastatin, a cholesterol-lowering drug. By mining search queries on Google, Bing, and Yahoo Search from 2010 White et al (2016) found that people who searched for both drugs were also more likely to search for terms related to the adverse event than those who searched for only one of the drugs. Two main limitations can be identified: (a) access to data: search information was provided to the researchers anonymously by users who agreed to share their search history; and (b) the study referred to a known ADR. Similarly, Chokor et al. (2015) mined a variety of Internet data sources and search engines (mainly Google Trends and Google Correlate) for information on reactions associated with the use of two popular Major depressive Disorder (MDD) drugs, Duloxetine and Venlafaxine. Yom-Tov & Gabrilovich (2013) noted that web search queries are potentially more suitable for the detection of less acute later-onset drug reactions, as acute early-onset ones are more likely to be reported to regulatory agencies.

By and large, while new methods have proven advantageous in identifying previously unknown adverse drug reactions, they are effort-intensive and further scrutiny of the outcomes by medical regulatory authorities is required in order to extract valid ADR signals. It was further discovered that a different emphasis on the type of adverse events reported on social media exists, which suggested that social media may be a better source for ‘symptom-related’ or less ‘serious’ (non-life threatening or not requiring hospitalisation) than laboratory test abnormalities and ‘Serious’ adverse event. A systematic review conducted by Golder et al. (2015) sought to summarise the prevalence, frequency and comparative value of information on the adverse events of healthcare interventions from user comments and videos in social media. Researchers concluded that, although reports of adverse events are identifiable within social media, there is considerable
heterogeneity in the frequency and type of events reported, and the reliability or validity of the data has not been thoroughly evaluated. Adverse events identified via social media but not documented elsewhere also tended to be mild or related to quality of life’. Under-represented adverse events on social media in contrast tended to include laboratory abnormalities or effects requiring diagnosis from a healthcare professional. Serious or severe adverse events were also under-represented in social media.

6.2.5 The challenges of social media

Social media does come with challenges, though. It generates patient-centric data, which is unfiltered and unchecked, and can use the incorrect terms, or refer to diagnoses that are based on internet research rather than confirmed diagnoses from healthcare professionals. It also produces large amounts of raw data that is challenging to analyse. Limitations include difficulties in searching, the large volume of irrelevant data, issues surrounding lack of validation, the danger of misinformation and duplicate reports, etc. As SNSs vary in terms of their core functional building blocks (identity, conversations, sharing, presence, relationships, reputation, and groups), a profound understanding of their characteristics is required in order to develop strategies for monitoring, understanding, and responding to different social media activities (Kietzmann et al., 2011). For pharmacovigilance, this signifies that the degree of uncertainty and bias of each SNS needs to be taken into consideration. To realise fully the benefit social media have to offer requires careful combination of each of these data sources to generate significant signals (Sloane et al., 2015). While social media provide an opportunity to tackle existing biases in pharmacovigilance, this does not mean that social media are an unbiased medium. It is reasonable to expect that social media user bases are skewed in terms of age, gender, ethnicity and physical location.

Personal data protection

When data is collected from social media it is important to ensure that the process conforms to applying legal restrictions and that privacy standards are met (Lengsavath et al., 2016). As the number of actors engaging with SNSs and SNS data increases, so does the risk for potential privacy infringements. The increasing demand for data protection due to new technological applications and the necessity to reinforce users' trust in services provided by the public and private sector is inducing legislators to approve data protection laws or amend the existing
regulations in order to adapt them to the technological evolution and new challenges (Greenleaf, 2012) A **nonymous** environment refers to an online context in which the offline identity is displayed. He uses the term nonymous to contrast with an anonymous online environment, in which people do not have to display their offline identity. Social networking data will qualify as personal data insofar as they relate to an identified or identifiable individual. Although data from social networks is public, this fact does not deprive it from the protection offered by the data protection legislation. The processing of such data still needs to be fair and lawful. As a result, firstly, there needs to be a legitimate ground on the basis of which the data could be processed. While SNS offer a large and often untapped potential to identify safety issues, the appropriate and effective use of social media can be overwhelming. New regulatory paradigms are needed, in order to specify the limit of the industry’s responsibility in collecting and reviewing social media; clarify issues related to the “identifiability” of the reporter and patient in safety data obtained via social media; and specify acceptable practices for following up on potential signals identified.

### 6.2.6 The way forward

Unlocking the potential of social listening for post-marketing safety surveillance has the potential to strongly supplement pharmacovigilance based on traditional ADR reporting systems. Golder et al. (2016) note that the methods to incorporate these data into current systems are largely unexplored. Nonetheless, the value of mining social media for adverse event reports has not yet been established. Methods exist to reduce noise and make the data suitable for post-marketing safety surveillance. Big data cannot be considered a substitute for, rather than a supplement to, traditional data collection and analysis (Lazer et al., 2014). Additional research is needed to better understand the strengths, limitations, and best practices of these methods.

Social media presents new channels and methods that can enable pharmacovigilance to move away from traditional safety reporting methods towards more patient-centric models for reporting, analysing and monitoring of safety data. Essentially, in terms of safety research, social platforms allow for both **information pull** (social media listening) and **targeted investigations** (direct-to-patient research). Social media activities for pharmacovigilance by companies fall into three broad categories, **listening** (safety data reporting), **engaging** (follow-up) and **broadcasting** (risk communication), each with varying degrees of complexity, associated issues and requirements. Social media monitoring is expected to become a standard practice in
pharmacovigilance in the future. For this purpose a careful evaluation and assessment of the use of social media as a pharmacovigilance instrument is required and new data processing techniques and software tools and infrastructure adapted to the volume, velocity, structure and veracity of social media data. Already, Marketing Authorisation Holders (MAHs) are obliged by European law to establish and maintain a system for pharmacovigilance and record all suspected adverse reactions brought to their attention. This includes record suspected ADRs from digital media.
1. Introduction

During the past decade, our perspective across the medicines safety continuum has changed significantly, mainly due to the affluence of data and the affordances of advanced data analytics, allowing the transformation of large amounts of data into meaningful information and knowledge that can be applied to improve drug safety and operational performance. The effects of technology innovation permeate all aspects of an organisation’s operations (technological, structural, and strategic) as a new logic for organising emerges. Powell (1998) stresses that rather than being the vehicles for processing information, making decisions and solving problems, the core capabilities of organisations are based increasingly on knowledge discovery and knowledge creation. Pushed by science and technology innovations, the global pharmaceutical industry has undergone significant technological, structural, and strategic changes, which have significantly impacted the industry paradigm and the strategy logic of enterprises (Brännback et al., 2001). This trend is accelerating today under the force of continuous shifts and innovations in underlying science and technology. Basset et al. (2012) propose Pharma 3.0 as a new paradigm of extended collaborations to characterise future relationships between drugmakers and doctors with their patients in the light of Web 3.0 technologies (semantic search, cloud computing and mobile applications).

This third part of the Literature Review investigates and discusses the ramifications and prospects of collaborative innovation in the context of pharmacovigilance. Section 2 discusses the current approaches of collaborative innovation and co-operative models of organisation (2.1), and outlines the future of pharmacovigilance collaborations: social innovation ecosystem (2.2). The characteristics of the emerging ecosystem paradigm are discussed in Section 3.

2. Collaborative innovation

Pharmacovigilance can be described as a system, i.e. as the grouping together of relevant interrelated, interdependent or interacting elements, in order to serve a specific collective purpose of balancing its information-processing capabilities against task requirements (Tushman & Nadler, 1978), namely of accommodating the information-value chain within and between individual organisations. However, the emerging paradigm of pharmacovigilance is wider than
the current definition of a pharmacovigilance system, as “a system used by the marketing authorisation holder and by Member States to fulfil the tasks and responsibilities listed in Title IX and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance”. This limited definition fails to describe the increasingly **dynamic and expanding nature** of pharmacovigilance. Furthermore, the pharmacovigilance system cannot be examined solely under business or applied science terms as it shares some unique characteristics, namely due to its high degree of **regulation**. The interplay of stakeholders in the pharmaceutical market also has a commercial dimension, involving touching issues such as competition policies, market regulation etc. According to Hancher (2010) the European pharmaceutical market is characterised by three types of competition: therapeutic competition (denoting competition between new, patented, innovative products), generic competition (denoting competition that comes from generic or bio-similar, non-patented products) and intra-brand competition (usually, in the form of parallel imports of cheaper products from low-priced countries into higher-priced market). While this may affect stakeholder expectations and behaviours in the common space of pharmacovigilance, an **in-depth discussion of the pharmacovigilance ecosystem from a competitive industry point of view falls beyond the scope of the present study**. In the present context the pharmacovigilance ecosystem is examined from a **utility** perspective (as a collaboration space), focusing on its mission to ensure the high level of medicines safety and public health. Collaboration leverages knowledge, skills and resources among organisations. A 2010 report by the Collaboration Consortium discussed the **collaboration evolution curve** in organisations. Organisations embracing collaboration progress through three stages, in which they derive increasing business value from collaboration. The stages are Investigative (tentative use of collaboration), Performance (structured collaboration execution embedded in existing business processes), and Transformational (use collaboration to create new ways of doing business). Following the evolution of collaboration and the organisational structure of the pharmacovigilance system is discussed, moving from the current coordination-based pattern towards future integrated models.

### 2.1 The co-operative model for drug safety investigations

Traditionally, pharmacovigilance has been operated as a centrally supervised, co-operative effort involving both multidisciplinary and multi-stakeholder collaborations, as links need to be forged on different levels (between people, departments, organisations, agencies, and countries) and in
different areas (scientific, technical, and organisational). Commercial and non-commercial stakeholders work together to create strategies for the early identification and management of drug safety issues. Strict governance provisions exist. Federated facilities are centrally organised as a single large-scale federated facility, based upon well-established standards and common platforms.

2.1.1 The integral role of pharmacovigilance in pharmaceutical organisations

With the application field of pharmacovigilance changing from one that is focused on case processing and compliance with reporting obligations, to one that is more comprehensive and cross-functional, inclusive of end-to-end risk/benefit assessment and risk management during the whole product life-cycle, the scope of pharmacovigilance within organisations has greatly increased (Clement, 2016). Mann & Andrews (2007) called for increased awareness within companies to develop issues management strategies, bringing together all relevant company resources. Clement (2016) notes that over the last decade significant transformations occurred regarding the role of pharmacovigilance departments play in pharmaceutical organisations. Pharmacovigilance departments must know about activities beyond their direct influence (e.g. information about product licensing). This means that their activities must cover the whole life cycle of medicinal products, coordinating their efforts with clinical and medical affairs, and contacting relevant departments and/or affiliates. Other important trends include outsourcing. The main drivers for outsourcing pharmacovigilance activities are flexibility and costs. As companies of any size will face significant fluctuations of the case inflow in their lifetime, in particular when a new drug gets approved and launched. In this context, Digital Medicines companies have emerged, operating at the intersection of the pharmaceutical industry and the information technology (IT) sector, to help with problems such as medication adherence or patient compliance, health monitoring, and patient engagement (Jawadekar, 2016).

Pharmacovigilance partnerships

A complex and vital relationship exists between wide ranges of partners in the practice of drug safety monitoring. Pharmacovigilance builds on a cooperative and proactive relationship between medicines manufacturers, regulatory authorities, etc (Mann & Andrews, 2007). According to the WHO (2004) key partners in the process of monitoring the safety of medicines include: government, industry, hospitals and academia, poison information centers, health
professionals, medical and pharmaceutical associations, patients, consumers, media and international regulatory organisations (EMA, WHO etc) public institutions and contract and research organisations (CRO) involved in research in pharmacoepidemiology and pharmacovigilance (van Leeuwen et al., 2016).

2.1.2 Stakeholders’ perspectives
The needs and interests of the involved stakeholders need to be consolidated. Effective collaboration and sustained commitment are vital to meet emerging challenges in pharmacovigilance. The principal stakeholders include: National regulatory authorities, National pharmacovigilance centres, and Drug developers and Market Authorisation Holders. Each of these stakeholders is set to perform its specified functional role in a dynamic and coherent inter- and intra-integrative manner within the environment itself. The work of National regulatory authorities revolves around the assessment, licensure, control, and surveillance of medicinal products are major challenges for national regulatory authorities confronted by a steadily increasing number of novel products, complex quality concerns, and new technical issues arising from rapid scientific advances. With the growing market globalisation, the volume of medicinal products crossing national borders continues to rise, and it is critical that regulatory knowledge and experience concerning medicines use can be shared, and that approaches to their control can be harmonised. National pharmacovigilance centres are governmentally recognised centres (or integrated system) within a country with the clinical and scientific expertise to collect, collate, analyse and give advice on all information related to drug safety. Drug developers and Market Authorisation Holders play active role in drug safety surveillance. They collect, collate, validate and follow up (SAEs) of all reported suspected adverse events, screen for adverse events; submit PSURs, perform post-authorisation safety studies, regularly check risks and benefits and plan mitigation actions. Working in the direction of supporting stakeholders’ work in the domain of pharmacovigilance, dedicated networks have been established. For example, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) has been established, coordinated by the European Medicines Agency (EMA), bringing together public institutions and contract and research organisations (CRO) involved in research in pharmacoepidemiology and pharmacovigilance.

Beyond guidance networks, new complex value chains are emerging. Pushed by advances in the medicines safety data continuum, the classic, linear information value chain has evolved into
a complex value network of partners participating in a common process. The joining-up of offerings from dispersed authorities can bring significant advantages. Partnerships include: government, national and international regulatory agencies, other competent authorities and private organisations, and pharmaceutical enterprises. In addition to opportunities, the increasing interconnectedness also creates limitations and requirements that need to be addressed. The correct management of information and its quick and efficient distribution among stakeholders (policy makers, regulators and pharmaceutical industry) are becoming prerequisites for quality. This however implies the seamless integration of information from different health information levels (tissue & organ, patient, disease, public health) that is stored in distributed repositories under the authority of different organisations. Drawing a parallel to the “connected enterprise” paradigm in the business domain, it can be concluded that drug safety investigations increasingly resemble to business processes that transcend the traditional boundaries of participating organisations. The challenge is to facilitate cross organisation collaboration on capability development in multiple dimensions for the successful implementation of federated drug safety investigations. In analogy to Rogers & Bozeman’s (2001) categorisation of research collaborations as “knowledge value collectives” and “knowledge value alliances”, two types of interaction can be defined among pharmacovigilance stakeholders:

● **Collaboration**: an arrangement between stakeholders having a joint interest to act together in a project. The legal responsibility of the project is endorsed by a single party. Roles are distributed between parties. Because collaborations have usually a very specific scope (e.g. conduct of a study), they are usually time limited.

● **Partnership**: an arrangement between several stakeholders having a common vision/mission and shared goals. A governance structure is created to establish shared decision-making. All partners have the right and the responsibility to participate and are affected by the benefits and other consequences arising from the partnership. The responsibility of the project is legally endorsed by all governance partners. Roles, resources and/or financial investments are shared between parties. Partnership structures are more complicated to set up and they are usually used for longer terms initiatives with broader objectives including the management of an array of studies.

The three principal enablers of collaboration in organisation are people and culture; processes and governance; and technology. Collaboration in organisations can be investigative,
performance-driving (structured collaboration execution embedded in existing business processes), and transformational (use of collaboration to create new ways of doing business). The process of aligning collaboration with an organisation’s strategy is an on-going activity, as requirements and priorities evolve with a changing environment. In line with the scope of collaboration, the setup of the interaction process may be formal (top-down and well prescribed) or investigative (bottom-up and tentative). Early implementations of pharmacovigilance are exploratory and agile, i.e. more adaptive rather than predictive, and output-oriented rather than process-oriented (Sidky, et al., 2007). They follow the project approach (Wijnen & Kor, 2000; 2007) with coherent sets of planned, non-routine based activities that aim to achieve a unique objective for a finite number of resources, separate from the standard organisational hierarchy. Subsequently, as effective projects become routine operations, concrete planning and control infrastructures are established.

In pharmacovigilance insight/decision making is based on the expert information processing model, which puts emphasis on the use of already developed deep knowledge of experts that complements computational information processing (Lord & Maher, 1990). Experts have the required knowledge base, acquired through experience, serving as a resource to tap into during information processing. Individual memory systems, comprised of individual areas of expertise as well as knowledge on “who knows what”, constitute a structural (“knowledge”) component of a transactive memory system. Communication processes among group members constitute a process component (Wegner et al. 1985; Wegner, 1995). Cognitive interdependence among participants exist, denoting that individuals rely on each other for being experts in certain knowledge domains and individual outcomes depend partially on what others in the group know. A network of collaborating experts represents an organic structure (Donaldson, 2001). Viewing technology from the perspective of collaboration, Thompson (1967) distinguishes between three types of technologies: mediating, long-linked, and intensive, with each type corresponding to specific types of interdependence between organisational entities: pooled, sequential, and reciprocal.

The current environment for pharmaceutical organisations is one that is characterised by uncertainty and continuous change. This rapid and dynamic pace of change is forcing organisations that were accustomed to structure and routine to become more agile and learn to improvise solutions quickly and correctly. To respond to this ever changing, dynamic
environment, organisations are moving away from the structures of the past that are based on hierarchies, discrete groups and teams and moving towards those based on more fluid and emergent organisational forms such as networks and communities. Drug regulatory agencies are increasingly pressed by the challenge of finding the appropriate balance between the need for rapid access to new drugs and the need to ensure comprehensive data on their benefits and risks. The quality, safety and efficacy of drugs are under constant scrutiny, as underlined with the evolution of the regulatory model from a one-off marketing authorisation to a life-cycle approach. (Eichler et al., 2008; Eichler et al., 2010). While signal detection and analysis remain the focal point of pharma safety systems, there are other aspects of drug safety that have been rather neglected until now, which should be included in monitoring latent and long-term effects of medicines, namely: the detection of drug interactions; measuring the environmental burden of medicines used in large populations; assessing the contribution of ‘inactive’ ingredients (excipients) to the safety profile; comparing safety profiles of similar medicines; surveillance of the adverse effects on human health of drug residues in animals, etc. Pharmacovigilance represents a flexible system: a dynamic set of interrelated components working together with the common objective to achieve a stated purpose or fulfil a designated need, building on an extended community of stakeholders. Third parties with an interest in drug safety information (e.g. healthcare practitioners for the purposes of improving clinical practice) need also to be regarded as stakeholders. The emerging paradigm of pharmacovigilance could be describes as social innovation, taking place within an extended ecosystem.

2.2 The future of pharmacovigilance collaborations: social innovation ecosystem

Responding to this trend an alternative vision for the future would be that of a self-organising research federation. In the social innovation ecosystem paradigm, pharmacovigilance would become a collection of different, dynamic and flexible resources interacting with each other and autonomously creating new insight regarding pharmacovigilance or building on drug safety information. Driven by growing market challenges, organisations in the business domain have evolved from being vertical, isolated and business unit-centric during the early years, to horizontal business-process-focused structures during the 1980’s and 1990’s, and towards a new ecosystem business paradigm (Moore, 1993, 2006) that features componetised and distributed business services (Endrei et al, 2004). According to Soren, Elena, Jeremy, Gustavo and Joseph
(2001) this new business ecosystem is characterised by the creation of virtual organisations, as opposed to vertically integrated structures, the formation of cross-organisational partnerships and the outsourcing of noncore activities. According to the Encyclopædia Britannica, an ecosystem is “a functional unit or complex of relations in which living organisms) interact with one another and with their physical environment, forming a dynamic yet broadly stable system” (Epstein, 2016). Central to the ecosystem paradigm is the notion of component interdependence and unity: the structure and functioning of the unit as a whole. Each species fulfils a specific function within an ecosystem and depends on its interactions with the other components for its survival. In the business domain, the ecosystem paradigm is characterised by shared business processes that eliminate organisational boundaries, consistent shared information, (vertical) industry standard services, shared infrastructure protocols, gateways, management environment and Collaboration architecture. The essence of a business ecosystem is that networks between companies need to be analysed from a higher conceptual level rather than from the viewpoint of individual organisations. Accenture’s latest trends report (2017) notes that companies are increasingly integrating their core business functionalities with third parties and their platforms, stating that business ecosystems are the foundation for companies to design future value chains that will transform their businesses, products, and even the market itself. Moore’s definition of the business ecosystem (1993), as a paradigm to describe economic coordination in a business sector, provides a conceptual high level ‘firm-centric’ view of competition and cooperation within a network of organisations that share a key technological platform. Its scope is the set of positive sum relationships (symbiosis) between actors. A co-evolution process is formed between networks of localised knowledge and trans-local knowledge networks (Doz et al., 2001). Firms’ capabilities co-evolve around new innovations. Valkokari (2015) distinguishes three different ecosystem types: business, innovation, and knowledge ecosystems. Knowledge ecosystems have their main interest and outcome in creation of new knowledge through joint research work, collaboration, or the development of knowledge base. They revolve around knowledge exploration and are characterised by decentralised and disturbed knowledge nodes establishing synergies through knowledge exchange (Valkokari, 2015). Estrin’s model of an innovation ecosystem (Estrin, 2009) recognised that the balance and constant interaction of various actors enables the cross-pollination of ideas and facilitates innovation. This model includes three
communities (research, development, application) which are embedded in a supportive structure made up of leadership, funding, policy making, education and culture. Furthermore, the social system of pharmacovigilance can be seen as an open innovation system, in which multi-minded stakeholders jointly design a future they desire (Gharajedaghi, 2006).

3. The pharmacovigilance ecosystem

The drug safety innovation landscape is already showing signs of a gradual evolution into an ecosystem, shifting its methods, processes, cultural habits and competencies from episodic management of drug safety challenges to more holistic, continuum-oriented approaches. The field of pharmacovigilance can be described as a knowledge ecosystem, although market behaviour and economic coordination are also of relevance to the pharmaceutical sector. With drug safety representing the central platform, a pharmacovigilance ecosystem describes the structure and behaviour of a network of stakeholders and the ways individual organisations can flourish (i.e. achieve their mission with regards to pharma safety) in such an environment. Cross-continuum data analysis is not just about the development of data hubs. Innovation derives from harnessing the power of interconnected capabilities, thinking and effort.

The sophistication level of the interconnectedness can range from ad-hoc investigations (project-based approach) to federated organisation structures (some shared services, consistent information representations and processes) to seamless integration (ecosystem).

A medicines safety ecosystem can be described as the combination of knowledge creation capabilities around medicines safety data. In the context of an ecosystem, coevolution takes place between interconnected organisations due to the effect they have on each other. Faced with the increasing complexity of safety investigations, the sector needs to align key stakeholders (regulatory authorities, pharmaceutical enterprises, people) towards the common objective of medicines safety: creating mutually supportive initiatives, reducing collective inefficiencies and innovating, in a way that collective risks are reduced. Pharmacovigilance can be characterised as a case of mutualistic coevolution (Peltoniemi, 2006), comprising reciprocal relations where all the participants benefit from the interaction and change in the direction of better compatibility. In this light, tighter integration, parallel change, better compatibility and complementary capability of all the participants will promote the coevolution of the whole system (Ning, 2016).
Since its early days the sector has been and continues to be highly regulated (Shorthose, 2014). However, emerging innovations permeate the entire ecosystem, pushing stakeholders towards new lateral synergies and the joint exploration of innovative evolutionary paths. As the system boundaries are expanding, pharmacovigilance becomes both the end and a service to third parties (e.g. timely medicines safety information utilised in the context of therapy). Stakeholder relationships within the pharmacovigilance ecosystem can be conceptualised as symbiotic network (Etemad et al., 2001), traditionally dominated by strictly regulated exchanges (in the context of approval, post marketing reporting and risk planning), but showing increasing evidence of lateral relationship building (e.g. relationships to CRO and other research organisations) and public-private partnerships (in the context of dedicated networks, and research projects and initiatives). The pharmacovigilance ecosystem is an open ecosystem, i.e. open to outside influences and surrounding ecosystems, as it influenced by technology innovations and social changes, responds and contributes to changes in other domains.

The design and deployment of pharmacovigilance systems should align the requirements of drug safety studies with technology structures and resources. In addition to the identification of activities, support for the interdependence of the organisations that support it, should be provided. In this context, both technical and social (co-operational) boundary resources need to be investigated and provided. The former refers to the means of exchange, i.e. to external “platforms” jointly utilised by stakeholders for developing complementary innovations. The later comprises organisational, legal and other “soft” aspects. “Collaboration impact zones” are described as those junctures where interactions and the exchange of expertise and information are frequent, urgent, and complex: these may be focused on either internal or external collaboration. Important aspects of an ecosystem include actors (species), relations between actors (network), performance (health), dynamics (evolution), and strategies and behaviour of actors (roles). In the case of pharmacovigilance, the health (performance) of the ecosystem is determined by the following four factors: value (niche creation), critical mass (robustness), continuous performance improvement (productivity) and co-evolution or the joint learning and optimisation effects. The expansion of the ecosystem though the addition of new network members create and share value. Typically, this is achieved by creating a platform whose value increases rapidly when the number of ecosystem members that support the standard goes up. While there exist no competing behaviours as in the case of a purely business ecosystems, some
stakeholders hold a dominant position in the pharmacovigilance ecosystem as well. Pharmacovigilance systems must support these collaborative requirements with **flexible business models**, taking into account the boundaries, effects of networks, changing responsibilities, etc, while at the same time enabling smooth crossing of these boundaries regardless of IT systems, corporate, or other boundaries. An environment to support innovation for the purposes of pharmacovigilance should allow to:

- Align collaboration with the investigation priorities;
- Build collaboration process and governance models to sustain co-operation;
- Create a technology plan that enables the collaboration vision to be realised;
- Cultivate collaboration practices by promoting a collaborative culture.

The Collaboration Consortium (2010) describes collaboration according to criteria that take into account the human behavioural aspects of collaboration: stakeholder Reach: (reaching the right communities and the right experts); richness of information, openness of collaboration and speed of output generation. The ability to diffuse knowledge and learn requires a wide range of inter-organisational linkages (Powell, 1998). Within the pharmacovigilance network, participants are contributing and integrating information and knowledge, in order to generate new knowledge about medicines safety and medicines safety-related areas. Knowledge creation is a learning process. The **development of new investigation practices can be described as an expansive learning cycle taking place in an extended organisational setting**, as described by Engeström's theory (Engeström, 1999). Engeström views learning as an expansive process: individuals question the accepted practices, and this initiates new learning cycles within the activity system.
Part D: The information value-chain

1. Introduction

Medical and healthcare research is currently on a transformation path. Technology is advancing at an unprecedented rate, with a catalyst effect on research and development in the field. As information and communication technologies (ICT) continue to evolve, data volumes are growing at exponential rates, with technology facilitating the generation, collection, storage, management, processing and interpretation of large amounts of data. Datafication is rendering information from every area of life into computerised data formats and transform it into new forms of value (Cukier & Mayer-Schoenberger, 2013). Medical and healthcare research are increasingly benefiting from the trend towards digitalisation and datafication, which, coupled with advanced mining and big data analytics techniques, allows for the creation of new knowledge and insight (Tresp et al., 2016; Fang et al., 2016). At the same time the digitisation of healthcare data and the corresponding information services are evolving into increasingly complex ecosystems. Research is faced with the collection and management of large amounts of complex structured and unstructured data (Big Data), and the need for advanced analytics methods in order to extract value. Data generation is massive and also pervasive. In addition to purposely created data (e.g. EHR), today there is a growing trend towards passively captured data, as individuals use cloud and client computing on smartphones and tablets, social media applications, wearable tracking equipment, connected health devices and sensors etc (Raghupathi & Raghupathi, 2014).

At this backdrop, research and innovation in medical and healthcare research takes the form of an information-driven value chain, involving a wide stakeholder community with varying perspectives and needs. The predominant aim to leverage all available data and information assets to meet defined research objectives, should be met with a cautious examination of the data value chain, its requirements and implications. Realising the full potential of novel technologies is a challenging task. Nonetheless, this is not a strictly technological challenge, but rather implies shaping a vision for information-driven research that recognises the complexity and limitations of the sector, the varying stakeholder perspectives and the exchanges and transformations that have to occur, in order to achieve the desired objectives. The field of
pharmacovigilance has received considerable criticism by stakeholders. In the EU, efforts to harmonise the domain have been criticised at various levels: by the industry (considering the current regulations to be fragmented, contradictory and unclear) and also by patient organisations and some national regulators claim that the current system is not sufficiently transparent or sufficiently independent from the interests of the industry. (Bendall, 2004; Permanand et al., 2006). The use of technology is not ethically neutral (Laudon, 1995). This is particularly the case with healthcare-related data, the exploitation of which contains ethical implications in its very design. The very changes that technical innovation can bring to medical and healthcare research also create ethical issues and challenges that need to be addressed. Ethics essentially refer to human values and describe “the right” and “the wrong” according to shared cultural value systems and existing social agreements. Ethics represent an important dimension of all services involving datafication and/or the digital transformation of data. The term Digital Ethics refers to the moral management of the human implications of digital developments, and most often to ethical issues associated with digital media (Ess, 2009).

When embarking on a research investigation, in addition to assessing the suitability of potential methods and technologies from a scientific point of view, one should also examine whether and to which extent their properties support or hinder human values (Stahl et al, 2014). Several ethical questions are raised with regards to the electronic investigation of a research question in the field of healthcare and life sciences: the ethical dimension of the research environments investigating medical and healthcare questions should be under intense scrutiny during the design stage and under constant monitoring during usage (Lee & Gostin, 2009), particularly the relationships between human rights, investigation protocols and methods, processes and tools. Starting from this point, the present section discusses the ethical ramifications of the creation of a research ecosystem that builds on the integration and processing of medical and healthcare data from a range of sources. The key to understanding this process is to take a focused look at each stage of the data lifecycle and investigate the ethics of methods, systems and services designed to collect, store, manage, exchange and process data against the perspectives of the involved stakeholders. Section 2 provides an overview of ethics and ethical considerations that permeate the use of technology and information systems in particular. Section 3 delves into the information-driven investigations in the field of healthcare where we propose a structured approach for the identification of relevant ethical issues across the data value chain. The paper
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attempts to provide a critical description of the problem and not produce a catalogue of prescriptive or proscriptive conditions. The approach however allows for the instantiation of concepts and can be a useful tool for aligning research requirements with human elements, technologies and in a more comprehensive way. Section 4 includes some concluding remarks regarding the ethical ramifications of information-driven investigations in the field of medicine and healthcare.

2. Ethical considerations in digital environments

During recent decades technology has changed virtually every aspect of life. With significant ethical considerations surrounding the use of technology, the relationship between technology and ethics holds an important place in scholarly research. Ethics comprise a set of values or moral principles, as well as the decisions, choices and actions we make that reflect and enact these values. In principle, the field of ethics involves systematising, defending, and recommending concepts of right and wrong behaviour (Fieser, 2016). From a pragmatic point of view: ethics describe a set of standards of conduct that guide decisions and actions based on duties derived from core values. Determining what is ethical is not just an individual decision, but can also is determined societally, or collectively (e.g. organisational Code of Ethics or Code of Conduct) Bowie (1997), Boatright (1997) McCollough (1991). Ethical principles provide a framework within which particular ethical issues can be analysed and resolved, and serve as basis for the development of specific rules or norms that can be applied in practice. Applied ethics examine and prescribe what a person is obligated or permitted to do in a given domain. Normative ethics focus on the drivers of ethical action, and how a person should act from a moral point of view. The aim is to arrive at moral standards that regulate right and wrong conduct (Ross, 1930). The term human rights has been coined to refer to rights (moral principles or norms) that are inherent in human nature and without which we cannot live as human beings. Human rights are regularly protected as legal rights in national and international law. A milestone document in the history of human rights is the 1948 Universal Declaration of Human Rights (UDHR) of the United Nations. The UDHR identifies dignity, liberty, equality, and brotherhood as key ethical principles. The Charter of Fundamental Rights of the European Union (2000/C 364/01) defines values and principles under six categories: Dignity, Freedoms, Equality, Solidarity, Citizens’ Rights, and Justice. Specific provisions are included
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regarding the fields of medicine and biology, among which the respect of the free and informed consent of the person concerned. Similar universal provisions are included in the European Convention on Human Rights (ECHR), an international treaty drafted in 1950 by the Council of Europe, set up to protect human rights and fundamental freedoms in Europe. Ethics are application- and context-specific: e.g. medical ethics (Garrett et al., 2001), clinical ethics, public health ethics (Harris, 1999), bioethics (Gert et al., 1997). For a given application case, potential ethical implications need be investigated to first derive relevant ethical principles and then operationalise them in the form of rules or norms that can be applied in practice. According to Beauchamp and Childress (1979), there are four prima facie duties or principles in biomedical ethics: Respect for Autonomy, Nonmaleficence, Beneficence and Justice. In 1964 the World Medical Association (WMA) has developed the Declaration of Helsinki (the Helsinki Code) as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Council for International Organisations of Medical Sciences (CIOMS) produced guidelines for biomedical research involving human subjects in 2002 (CIOMS, 2002; 2016) and for epidemiological studies (CIOMS, 2009), which they are presently in the process of unifying. In 2011, the World Health Organisation (WHO) produced a compilation of 10 standards applicable for the ethics review of health related research involving human participants (“Standards and operational guidance for ethics review of health-related research with human participants”) (WHO, 2011). In 2001, the EU developed the Clinical Trials Directive (Directive 2001/20/EC) on the approximation of the laws, regulations and administrative provisions of the Member States relating to implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. This was concretised further by the Good Clinical Practice (GCP) Directive (Commission Directive 2005/28/EC of 8 April 2005), which lays down “principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products”. In 2005, UNESCO (the United Nations Educational, Scientific and Cultural Organisation) adopted the Universal Declaration on Bioethics and Human Rights (UNESCO, 2005), which addresses ethical issues related to medicine, life sciences and associated technologies as applied to human beings, taking into account their social, legal and environmental dimensions. Aiming to set out common general standards for the protection of the dignity of the human person in relation to
biomedical sciences, the Council of Europe developed the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (Oviedo Convention). This treaty, which was opened for signature in 1997, is an international instrument aiming to prohibit the misuse of innovations in biomedicine and to protect human dignity. While the freedom of scientific research is recognised, precedence is afforded to the protection of human dignity and other fundamental freedoms. Research carried out on human beings is under strict controls.

**Digital ethics and data ethics**

In today’s technology-infused world, technology design needs to be ethically informed, as the use of technology cannot be considered as ethically neutral (Richardson, 2000). In ICT system and service development ethics take on a more practical view on the application of normative principles. Digital ethics deal with the moral management of the human implications and overall impact of digital developments, i.e. with human ethical behaviour when using digital devices (Haddon, 2016). In 1976, the term computer ethics was introduced by Walter Maner. Maner called for the creation of a separate branch of applied ethics, after noticing that, often when computers are involved in medical ethics cases, new ethically important considerations arise. Computer ethics is described as the analysis of the nature and social impact of computer technology and the corresponding formulation and justification of policies for the ethical use of such technology (Moor, 1985; Tippett, 2000; Bynum, 2000,2001; Himma et al, 2008; Floridi, 2010). In a narrower sense information ethics addresses ethical questions dealing with internetworked information and communication media. (Bynum, 2010) The terms cyberethics and Internet ethics have also been used to refer to computer ethics issues associated with the Internet.

An important area of digital ethics is Data Ethics, which is concerned with the moral governance of the integrity, handling, control, and provenance of data. Ethical data practices need to be implemented and enforced all along the data life-cycle, with strong controls during collection, aggregation, sharing, analysis, storage and disposal of data. In today’s connected information world, the term data protection - often used as an umbrella term for ethical data practices- represents a critical dimension of privacy. A distinction is made between public, private and personal data. Public formation is already a matter of public record or knowledge. **Personal data** is “any information relating to an identified or identifiable natural person (‘Data
Subject'); an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity” (Directive 95/46/EC). Personal data relates to a person’s private, professional or public life. It can be anything from a name, a photo, an email address, bank details, posts on social networking websites, medical information, or a computer IP address.

The protection of personal data is stipulated in the European Charter of Fundamental Rights and in Article 8 of the European Convention on Human Rights (Right to respect for private and family life). Elaborating on the subject, the 1980 privacy and data protection guidelines of the Organisation for Economic Cooperation and Development (OECD) defined the following seven principles: Notice, Purpose, Consent, Security, Disclosure, Access, and Accountability. The 1995 Data Protection Directive (Directive 95/46/EC) of the European Parliament and of the Council regulates the processing of personal data within the EU, namely the protection of individuals with regard to the processing of personal data and on the free movement of such data.

Personal data are defined as "any information relating to an identified or identifiable natural person ("data subject"); an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity". The Data Protection Directive defines three fundamental principles: transparency, legitimate purpose, and proportionality. Personal data should not be processed at all, except when these conditions are met. The latest General Data Protection Regulation (GDPR) (Regulation (EU) 2016/679), adopted in 2016 and set to replace Directive 95/46/EC, intends to further strengthen and unify data protection for individuals within the EU. New provisions include Privacy by Design and by Default (Article 25), i.e. that data protection is designed into the development of business processes for products and services.

The Council of Europe’s Convention for the protection of individuals with regard to automatic processing of personal data (Convention 108) (1981) laid down the basic principles of a lawful data processing addressing the threats from the invasion of information systems, such as the data aggregation. According to UNCTAD (2016) compatibility of national data protection policies is imperative but remains a challenge, namely in areas like: addressing gaps in coverage, assimilating new technologies, managing cross-border data transfers, balancing surveillance and
data protection, strengthening enforcement, determining jurisdiction and managing the compliance burden. In order to promote international compatibility, it is important to avoid duplication and fragmentation in the regional and international approaches to data protection, through the adoption of one global unifying initiative or by ensuring that regional initiatives are internationally compatible.

Particular attention must be paid to Health data: data concerning all aspects of the health condition of a person, both physical and psychological. Health data are considered to be sensitive data according to European law and its processing is prohibited as a general principle. This ban is not absolute and processing may be authorised in some situations, when there is consent of the holder of the data and additional data security measures are available, such as the logical separation between health data and other personal data. Data relating to health condition, sexual life or genetic data must be logically separated from other personal data. EU Directive 95/46/EC sets strict conditions for personal data use the purposes of preventive medicine, medical diagnosis, the provision of care or treatment, or the management of healthcare services.

3. Ethical Congruence of system design

Several transdisciplinary approaches have been proposed for supporting human values through system design. The socio-technical systems theory (Trist and Bamforth, 1951; Mumford 1995), recognising the existence of a two-way relationship between people and machines, argues that the effective design of technology-based work processes can only be achieved through the simultaneous optimisation of both technical and social elements. This needs to include an investigation of ethical implications. In this context social informatics deal with the study of information and communication tools in cultural or institutional contexts by taking an integrated look over the design, uses and consequences of information technologies (Kling et al., 2005, Kling, 2007). Adopting a bottom-up approach, participatory or co-operative design (Carroll et al., 2007) attempts to actively involve all stakeholders (e.g. employees, partners, customers, citizens, end users) in the design process to help ensure the result meets their needs and is usable.

Bringing ethics early into the systems design process, the value sensitive design (VSD) methodology for the design of technology, adopts the position that technologies provide value suitabilities that follow from properties of the technology. As a result a given technology is more suitable for certain activities and more readily supports certain values while rendering other
activities and values more difficult to realise. Value Sensitive Design proposes three types of investigations: Conceptual, Empirical, and Technical/engineering. **Conceptual investigation** entails a philosophically informed analysis of the central value constructs that are relevant, the identification of the stakeholders affected directly and/or indirectly, the human values implicated, the existence of competing values. Depending on the questions at hand, many analyses will need to be informed by **empirical investigations** of the human context in which the technical artefact is situated. **Technical investigations** focus on how existing technological properties and underlying mechanisms support or hinder human values. System design should be ethically-informed, that is it should be consistent and aligned with the intended values and ethical principles. To promote the **Ethical Congruence of designs**, investigation should view each step of the design process in conjunction with the values that apply and make appropriate decisions to bridge the gap between world of ideas and world of things.

### 3.1 Ethical considerations across the information value-chain

Medical and healthcare research is knowledge intensive and collaborative. Research and innovation take the form of an **information-driven value chain**, involving a wide stakeholder community with varying perspectives and needs. As data volumes grow through developments in technology and research and knowledge creation is increasingly tapping into new sources of information, at the same time it is moving away from the conventional model of independent, “all-in-one” research units and more towards dynamically interconnected research environments, where complex relationships and dependencies among stakeholders exist.

The digitisation of healthcare is creating an increasingly complex environment for medical and healthcare research. For example in the area of drug safety monitoring, while traditional investigation methods rely on health professionals reporting ADRs, in recent years this approach is being increasingly challenged by big data and crowd-sourced health. This explosion in drug and medical information includes studies, cases and informal sources of information such as media reports, scientific literature and websites. Also the empowerment of patients is producing a growing amount of data ranging from the direct patient reporting of ARDs (patient reported outcomes) to social media and social networks recording and discussing healthcare issues and treatments. Electronic medical records, patient inquiries on websites and search engines and other consumer-generated media are also potential sources of early signals regarding safety
issues. All these sources can potentially be mined for signals and/or for other evidence to support sense making and evidence creation in the context of post marketing drug risk/benefit analysis.

Typically, the life-cycle of business knowledge creation involves the following stages: Acquisition, Identification, Retention, Utilisation, Development, Sharing/distribution (Probst et al. 1999), whilst technologies associated with digital content include: database management systems, content storage systems, indexing and search technologies, metadata technologies, workflow engines etc. Pappa et al. (2009) described the most important stages of medicines knowledge management as: Knowledge Generation/Acquisition, Storage & Retrieval, Distribution and Presentation, and Sharing, and also stressed the importance of knowledge in people (tacit knowledge). According to Nonaka (1994), discussion and dialogue is the central method to increase knowledge distribution, including tacit knowledge. Effective KM must include tools for promoting the socialisation of tacit knowledge: opening lines of communication, focusing on better cooperation and synergy between all the different actors and catering to their diverse interests and needs. Groupware applications and collaborative systems (such as videoconferencing tools, online forums, shared authoring tools, instant messaging, electronic whiteboards etc) that facilitate networked group collaboration (virtual groups) represent potential enablers for the KM process.

Focusing specifically on big data and emphasising the distributed and often heterogeneous nature of data, IBM describes the data lifecycle for value creation as the sequence of steps. Relevant data sources are located and evaluated for cost, coverage, and quality (Discovery). Data is then ingested into the evidence creation environment (Ingestion), where it is transformed into usable formats through processing (Processing) and possibly stored for future use (Persisting). Much of the value in big data can be found from combining a variety of data sources (Integration). Analysis work takes a combined look over data to derive new insights and evidence (Analysis). The results are reported to the organisation in a way that makes them useful for value creation (Exposure). A typical study process comprises the following three stages: planning, implementation (sourcing and execution) and presentation. An overview of the evidence creation process is provided in Figure 4:
For instance, the ADVANCE project, which revolves around healthcare databases federation for vaccine safety signal detection, proposed a distributed collaborative information generation workflow, including the following stages: Protocol Development, Data Extraction, Data Transformation, and Analysis, Report & Archiving. **Protocol development** starts with scoping: shaping of the information that is needed to develop the objective and design, as well as feasibility assessment. Scoping is the first step prior to protocol writing which in itself comprises of several steps from writing the protocol, defining outcomes, covariates and exposures, as well as obtaining approvals and registering of the protocol in line with the guidelines that apply for the specific type of study. **Data extraction** is the step where queries are launched on the original data source to retrieve study specific data (e.g. the vaccinations of interest, the population of interest for the study). **Data transformation** is the step during which the extracted data are transformed into an analytical dataset in line according to the study design. **Analysis** comprises of describing the data and further analysing them according to a statistical analysis plan.

Legal and ethical questions are raised throughout the process regarding the collection/management and use of information. Different information ‘producer’ and ‘customer’ segments exist and need to be accommodated. The study process taps into a variety of data sources, each pertaining to a different KM implementation and being managed accordingly. The
creation of knowledge requires the aggregation of data and information dispersed among various systems and repositories, to produce a distributed environment, in which data of medicinal interest can be processed and easily accessed by the different stakeholders in a transparent and secure way. Sources and data types include (Chen et al, 2016):

Table 12. Data sources [source Chen et al. (2016)]

<table>
<thead>
<tr>
<th>Data type</th>
<th>Data source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human-generated</td>
<td>Physicians’ notes, email, and paper documents</td>
</tr>
<tr>
<td>Machine-generated</td>
<td>Readings from various monitoring devices (e.g. remote sensors)</td>
</tr>
<tr>
<td>Transaction</td>
<td>Billing records and healthcare claims</td>
</tr>
<tr>
<td>Biometric</td>
<td>Genomics, genetics, heart rate, blood pressure, x-ray, fingerprints, medical images etc.</td>
</tr>
<tr>
<td>Social media</td>
<td>Interaction data from social websites</td>
</tr>
<tr>
<td>Publications</td>
<td>Clinical research and medical reference material</td>
</tr>
</tbody>
</table>

As noted by Raghupathi & Raghupathi (2014), the complexity begins with the data itself. Data can be structured, unstructured or semi-structured, stored in different formats and systems, in multiple locations, originating from internal and external sources, managed and owned by different providers. The ethical considerations associated with each information stream permeate and condition the entire knowledge creation value-chain. Issues like ownership, governance, privacy and security have to be addressed across the information pipeline. As emerging technologies constantly create new options for knowledge capturing, organisation and storage, retrieval and distribution, processing and analysis, and enable the establishment of new knowledge value chains, new requirements are raised for the development of pervasive control mechanisms over the use of data throughout the information supply chain. Ethical issues need to be investigated from a variety of viewpoints and consolidated across the value-chain.

While currently, most strategies emphasise issues like data privacy, digital ethics requires a broader consideration, also encompassing the provenance of data, their life-cycle across the pipeline and the operational processes where it is applied to affect real-world outcomes. Drawing from the field of Digital Rights Management (DRM), which relates to the persistent protection of digital data within business operations and includes “all technologies and/or processes that are applied to digital content to describe and identify it and/or to define, apply and enforce usage rules in a secure manner” (WIPO, 2003) and deals with the persistent protection of content, tracking access and operations on content, the definition and implementation of contract rights to content (rights licensing), as information flows across the pipeline, ethics should examine (a)
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the digital content to be protected, (b) the holder of rights to this content, who could be affected/harmed by data misuse (c) the end-user, to whom a right to “consume” this content is granted, and (d) the usage rights that determine what the end-user can do with the content.

Content is intended for consumption by specific individuals, groups or organisations. Only authorised users are allowed to create, store, access, manipulate and communicate information objects within or across organisational boundaries, depending on their business role and authorisation rights. Rights are defined through organisational regulations, laws and agreements and can be acquired automatically (e.g. authorisation rights pertaining to a specific business role are automatically passed to the individual holding this position) or distributed (e.g. by contract).

Information systems for medical and healthcare research act as intermediaries, not only facilitating content brokerage, exploration and analysis, but also providing an innovation arena for networking and collaboration among stakeholders. The management of knowledge thus entails both a technological and an ergonomic dimension: The first perspective views KM as an object that can be captured, transferred, and processed with technology as the key enabler for knowledge collection and distribution, while the second views KM as an interpretation process that relates to each individual. In this sense, both medicinal data and knowledge in people represent knowledge assets to be managed effectively. An information-value chain raises many moral and ethical issues that relate to both types of knowledge assets.

Following, a structured approach is proposed for the identification of relevant ethical issues across the data value chain. The EU Directive 95/46/EC places the responsibility for compliance on the shoulders of the "controller", meaning the natural or artificial person, public authority, agency or any other body which alone or jointly with others determines the purposes and means of the processing of personal data. In this instance the significance of the term processing is quite broad, meaning "any operation or set of operations which is performed upon personal data, whether or not by automatic means, such as collection, recording, organisation, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combination, blocking, erasure or destruction. In essence, ethical requirements call for the implementation of measures and controls across the pipeline. Within the typical flow of information (Figure 5), there is interplay and succession of a variety of stakeholders. At each step, the digital content to be protected changes, as does the holder of rights to this content, the user of content to whom a right to “consume” this content is
subsequently granted, and the usage rights that determine what this user can do with the content. At any given stage of the value-chain, all involved stakeholders need to be aware of who the rights holders are, which rights are concerned, as well as the extent to which some rights might be relaxed to permit certain uses. Policies, procedures, organisational structures and software and hardware functions need to be in place in order to enforce these provisions.

Figure 5: the flow of information across the value-chain

Drawing from the Zachman Framework (Sowa & Zachman, 1992; Zachman, 2003), a two dimensional classification scheme for descriptive representations of an enterprise, in the following paragraphs we analyse ethical considerations across the information value-chain from a contextual perspective. The Zachman framework provide a holistic view of the system, proposing six different analysis perspectives as part of the transformation of abstract ideas and concepts into an instantiation: the upper transformations represent high-level views of the enterprise, while the lower rows generally represent views that require additional detail. The six cognitive abstractions discussed by Zachman are: What, How, When, Who, Where, and Why. In the present context, each question primitive targets an important aspect of ethical analysis: ‘What’ is concerned with ethically sensitive artefacts (data and knowledge assets), ‘How’ with process or function (protection policies and measures), ‘Who’ with information about stakeholders (actors in the process), ‘Where’ with location (the stage in the value chain), ‘When’ with time cycle related information (time-point) and ‘Why’ is concerned with motivations and objectives.
2.1.1 Data sourcing: Data creation and storage

At the start, and holding a prominent place in the process, is the data producer (data originator) who creates, collects or reports information about the patient (data subject) and/or medical science and healthcare. The data originator is typically the patient, a physician, a health practitioner, a scholar, an organisation etc., who directly or indirectly produces data of medical interest. Overall, there is a growing diversity of medicinal data stakeholders (creators, owners, managers and users), data sources and data types.

Data ownership refers to the issue of defining and providing information about the rightful owner of data assets, and to the acquisition, use and distribution policy implemented by the data owner. (Cuzzocrea, 2016). Personal data, in particular, must be in control of the owner and must not be communicated to third parties, unless the holder of the data expressly consents through a free informed will. EU Directive 2001/20/EC stresses the need of having a signed informed consent from participants, defined as informed consent: decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative. Informed consent is the process by which a participant needs to be fully informed about the research in which they are going to participate in. It originates from the legal and ethical right to self-determination, the right of the participant to direct what happens to their body and personal data, the right to be free from (bodily) interference and also from the ethical duty of the investigator to involve the participant in the research. In some cases consent can be implicit. For example, the UK government introduced an electronic health record scheme for the entire population of the country on the basis of implied consent, i.e. patients are assumed to agree to the creation of a record unless they refuse. (Wadhwa & Wright, 2013). In some cases data is collected from unconsented patients, leading to ethical and governance challenges (Denaxas et al., 2016). When data is not obtained fairly, the resulting research work is controversial, as it is not in conformity with ethical restrictions.

According to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects: “medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications”....”In medical research involving human subjects, the well-being of the individual research subject must take precedence
over all other interests”....”It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects”... “Participation by competent individuals as subjects in medical research must be voluntary”...”Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimise the impact of the study on their physical, mental and social integrity.”

When data is collected across diverse media it is important to ensure that the correct protocols apply (Lengsavath et al., 2016). The use of biosensors, wearables, smart phones, smart watches and other monitoring devices allows physicians to monitor a wide range of physiological attributes of the individual in-hospital, in-home or on-the-go (Appelboom et al, 2014; Ha,2015; Lloret et al., 2013). This allow for the collection of data regarding health and physiological conditions (e.g. blood pressure, heart rate, body temperature, facial expression and even behaviour, emotions, etc) but can also address other aspects of life, like the activities or the geographical position of the individual. Monitoring produces a blurring of the public and private spheres, and creates a danger of vigilance by other individuals or institutions. Intimacy and private life are to be protected, and warranties must be given on two different aspects: the right to protect personal information from being accessed by unauthorised third parties and the right to know what personal information is retrieved by others. This is particularly the case when third party applications are used to collect patient data, or when devices that directly connect to the Internet or other insecure networks are employed in the process. It is thus necessary to provide the user with information about what personal information is stored, and why and whether the information is to be transferred, how and where. Specific conditions apply also with regards to medical devices and software applications used for the collection of data (e.g. sensors, monitoring devices), according to Directives 93/42/EEC and 2007/47/EC. Within a study, every system that is designed for diagnosis and/or therapy can therefore be considered as a ‘device intended for clinical investigation’. A fundamental requirement for conducting the study is that a “duly qualified medical practitioner” must be identified for the investigation. The four medical ethics principles proposed by Beauchamp & Childress (2001) are also relevant to the use of monitoring devices, particularly non-maleficence (the "obligation not to inflict harm"on patients) and respect for autonomy (the patient’s right of self-determination). Other than from the functioning of the device itself, harm to the individual may be caused by the disclosure of
confidential information (breach of confidentiality), e.g. the unintended disclosure of disease status. While devices become increasingly less obstructive, the threat of invasive monitoring remains, or of monitoring that undermines an individual’s freedom to behave the way they would normally do.

Research may focus on the Internet as source of information. **Internet-based research** is research which utilises the Internet to collect information through an online tool, such as an online survey; studies about how people use the Internet, e.g., through collecting data and/or examining activities in or on any online environments; and/or, uses of online datasets, databases, or repositories. (Buchanan & Zimmer, 2012). Ethical principles also apply in this case, calling for researchers to ensure the protection of individual privacy of subjects and the confidentiality of any data collected (AOIR, 2012). Viewing privacy mainly as informational privacy, with individuals having control over the publication and distribution of information about themselves, researchers should engage in data collection under controlled or anonymous environments, and remove Personally Identifiable Information (PII) from collected data (e.g. identifiers of physical location, internet log data etc.). Anonymisation provides a safeguard against accidental or mischievous release of confidential information. Yet, the threat of re-identification remains (Brownstein et al., 2006; El Emam et al., 2011; Richards & King, 2014). At any given step of the pipeline, provisions should be made to hinder the re-identification of presumed anonymous users so that individual identities and personal information are not revealed. This, however, could limit the availability of data for lawful secondary purposes (e.g. research).

There is growing interest in exploring the use of **social media (social listening)** in medical and health research, in areas like drug safety monitoring (active, real-time pharmacovigilance)(Dellavalle et al., 2009; Leaman et al., 2010; Lardon et al., 2015, Powell et al., 2016, Paul et al., 2016). With the increasing availability of advanced data scraping technologies, capable of automating and performing data collection from online platforms at a large scale, ethical questions are raised with regards to **web data scraping.** While much of the data posted by the patients is publicly available on the Internet, depending on the individual’s use of privacy settings when posting, provisions still need to be made in order to ensure their privacy, since personal data need to be processed in accordance with the rights of data subjects. “Data must be processed fairly and lawfully and must be collected for explicit and legitimate purposes and used accordingly” (EU Directive 95/46/EC). These conditions applied for example
when anonymised signals on drug interactions were mined from search logs (White et al., 2013). Again the consent of participating web users was sought: only web users who opted to share search activities could be included in the study.

Data collection or mining techniques used to collect or extract relevant information from data sources should take into account ethical concerns regarding the collected data. However, the legal framework supporting the implementation of ethical principles can act as a barrier, through its restrictiveness (adoption of extremely strict rules), its fragmentation (adoption of different rules and interpretations), or its uncertainty (adoption of unclear rules) (Future TDM, 2016).

**Ethical risks for data producers** include: **unauthorised collection of data, loss of privacy control, personal data security** or **misuse, improper practices**.

Research can also explore **Open Data**, defined by OKFN as a piece of data or content that “anyone is free to use, re-use and distribute it subject only at most to the requirement to attribute and/or share alike”. Open Data does not refer to personal or sensitive data that can be linked to individuals but only to non-personal data. Yet concerns about data provenance may be raised.

Data provenance concerns with the problem of detecting the origin, the creation and the propagation process of data within a data-intensive system. In 1996 the European Commission adopted Directive 96/9/EC (Database Directive), which harmonises the legal protection given to data stored in electronic databases in EU member states. The holder of database rights may prohibit the extraction and/or re-utilisation of the whole or of a substantial part of the contents: the "substantial part" is evaluated qualitatively and/or quantitatively and reutilisation is subject to the exhaustion of rights. The lawful user of a database which is available to the public may freely extract and/or re-use insubstantial parts of the database.

**Data custodians** are entrusted with the preservation of sensitive data, following the (explicit or implied) consent of the individuals. The term **big data** often used to describe medicinal data denotes “large pools of data that can be captured, communicated, aggregated, stored, and analysed” (Manyika, 2011). With regards to the storage environment, the preservation of the confidentiality, integrity and availability of information should be guaranteed (information security) (Cuzzocrea, 2014). The US Health Insurance Portability and Accountability Act (HIPAA) (1996) rules provide federal protections for patient health information held by Covered Entities (CEs) and Business Associates (BAs) and give patients an array of rights with respect to that information. Regulations include the Privacy Rule, which protects the privacy of
individually identifiable health information; the Security Rule, which sets national standards for the security of electronic Protected Health Information; and the Breach Notification Rule, which requires CEs and BAs to provide notification following a breach of unsecured Protected Health Information (ONC, 2015). Confidentiality involves ensuring that information is accessible only to those authorised to have access. Integrity involves safeguarding the accuracy and completeness of information and processing methods. Availability involves ensuring that authorised users have access to information and associated assets when required. Transparency of management of the collected data is imperative. Provisions should be made to ensure that the systems and policies comply with relevant legislation, regulations, agreements and contractual obligations requiring information to be available, safeguarded or lawfully used. Assurance as to compliance should be provided.

2.1.2 Research execution: Data aggregation and analysis

For the purposes of a research investigation (i.e. an investigation hypothesis based on a research/scientific protocol) attainable, relevant information items are brought together, analysed and synthesised to produce knowledge. Health data is considered to be sensitive and its processing is typically not authorised in all situations, with the exception that there is consent of the holder of the data and additional data security measures are available. The rights to be transferred by the data custodians (who are the rights holders at this stage) to the investigators for the purposes of their research work, need to be investigated, determined and formally agreed (Service Level Agreement) in the context of this dynamic investigation environment.

Data aggregators manage the retrieval of information from distributed information sources. Overall, doing studies that aggregate distributed data (e.g. about patients in different hospitals or countries) can be challenging. Data needs to be reliable, findable, accessible, interoperable and reusable. In many cases, the access to medical information is hindered not only by the non-interoperability or other technical barriers concerning the involved information and communication systems, but rather by the lack of agreed data governance and exchange provisions. An important challenge is the ethically-informed integration and exploitation of heterogeneous information silos, so as to enable the search and retrieval of usable information. Securing all aspects of computer systems and networks, including network devices remains key, also from an ethical point of view. Information security includes provisions for the software and
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the communications technology systems and networks for communicating and processing information, for example the use of technologies for secure transmission of potentially sensitive data (including SSL encryption of data as well as masking of IP addresses), so that a clear trust relationship is maintained at all times (Filkins et al., 2016). From a technical point of view, integration involves the interoperability of networks, information systems and data and knowledge repositories. On cybersecurity, the EU Directive on security of network and information systems (the NIS Directive) represents significant progress in creating a more robust legal framework for achieving and maintaining a high level of security of network and information systems across essential services. The sharing and exchange of data with third parties creates the need for processes for collecting data which typically are neither flexible nor rapid. The EU Directive 2002/58/EC on Privacy and Electronic Communications (E-Privacy Directive) regulates data protection and privacy in the digital age. Data exchange and usage is being reinforced through service and information interoperability initiatives, such as the eHealth European Interoperability Framework (EU, 2012) for the interoperability of clinical information, and health data standardisation efforts (CALLIOPE, 2010).

2.1.3 Processing and combination

The potential ethical risks from digital transformations and processing need also to be addressed. Privacy respecting analysis of sensitive data residing in distributed data repositories is a challenging task. The EU Directive 95/46/EC places the responsibility for compliance on the shoulders of the "controller", meaning the natural or artificial person, public authority, agency or any other body which alone or jointly with others determines the purposes and means of the processing of personal data. The data processor is defined as “the natural or legal person, public authority, agency or any other body which processes personal data on behalf of the controller”. In this context the term processing means "any operation or set of operations which is performed upon personal data, whether or not by automatic means, such as collection, recording, organisation, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combination, blocking, erasure or destruction". This definition is very broad and includes both “the processing of personal data wholly or partly by automatic means”, and also “the processing otherwise than by
automatic means of personal data which form part of a filing system or are intended to form part of a filing system”.

The protection of the rights and freedoms of data subjects with regard to the processing of personal data requires that appropriate technical and organisational measures be taken, both at the time of the design of the processing system and at the time of the processing itself, to maintain security and prevent any unauthorised processing. The Council of Europe’s Convention for the protection of individuals with regard to automatic processing of personal data (Convention 108) (1981) laid down the basic principles of a lawful data processing addressing the threats from the invasion of information systems, such as the data aggregation. Its purpose is to secure for every individual respect for his rights and fundamental freedoms, and in particular his right to privacy, with regard to automatic processing of personal data. The treaty acknowledges that the unfettered exercise of the freedom to process information may, under certain conditions, adversely affect the enjoyment of other fundamental rights (for example: privacy, non-discrimination, fair trial) or other legitimate personal interests (for example employment, consumer credit). It is in order to maintain a just balance between the different rights and interests of individuals that the convention sets out certain conditions or restrictions with regard to the processing of information.

In recent years the trend towards cloud computing enables ubiquitous, convenient, on-demand network access to a shared pool of configurable computing resources (e.g. networks, servers, storage, applications, and services) that can be rapidly provisioned and released with minimal management effort or service provider interaction. The processing of sensitive data in cloud computing environments, however, raises additional concerns and requires additional safeguards, e.g. as described in the Sopot Memorandum (International Working Group on Data Protection in Telecommunications, 2012) and the recommendations of the EU Article 29 Data Protection Working Party (WP29, 2012 & 2015). Potential risks identified in the Sopot Memorandum (2012) include: breaches of information security, such as breaches of confidentiality, integrity or availability of data, and violation of laws and principles for privacy and data protection etc., resulting from the controller losing control of the data and data processing, due to the involvement of cloud service providers and subcontractors.

There are also cases where data processing cannot be centralised: the data of interest is distributed across several databases, whose contents cannot be revealed to third parties. The
exchange of information between these databases is prohibited, as is the retrieval and aggregation of data at a central point, in order to perform operations on the data. This is a challenging problem calling for techniques that allow for secure multiparty computation. One such solution is distributed computation, which only reveals the answer to the question of interest, without any of the parties involved becoming aware of the specific information held in each other’s databases (Lindell & Pinkas, 2002)

In principle, Directive 95/46/EC prohibits the processing of health data. This prohibition applies to all personal data which have “a strong and clear link” with the description of the health status of a person and will include genetic data. Consequently third-party providers of distributed data processing operations are – as much as any other person processing personal data - subject to privacy and data protection regulations. They are subject to European regulations if they are storing personal data or processing these data in any other way. The confidentiality and security of processing: “any person acting under the authority of the controller or of the processor, including the processor himself, who has access to personal data must not process them except on instructions from the controller”. In addition, the controller must implement appropriate measures to protect personal data against accidental or unlawful destruction or accidental loss, alteration, unauthorised disclosure or access.

2.1.4 Reporting

Attention is required during the presentation of results, not only with regards to the protection of the intellectual rights of authors and collaborators (copyright issues), but also to the ethical rights of the data subjects. Depending on the purpose and the context in which research is carried out, presentation may take the form of a confidential report circulated within and providing insight to a closed circle of stakeholders, or of a public document (a research paper, an online or paper report, a newspaper article etc.). Researchers increasingly are able continue to collect detailed data about individuals from sources such as social media, blogs or public email archives, and these rich data sets can more easily be processed, compared, and combined with other data (and datasets) available online.

During the publication stage, contents might be disclosed to the public, included in the publication of the results, e.g. in the form of quotations or examples of data used. In such a case, the question raised is whether that would constitute the disclosure of sensitive information. In various cases, however, when extensive datasets have been released, researchers have been able
to re-identify individuals by analysing and comparing disclosed research datasets (Sweeney 2002; Schwartz & Solove, 2011). Researcher will always consider before publishing information—whether data contain combinations of such information that might lead to identification of individuals or very small groups. How much of this potentially identifying information can be safely included in data that is assumed to be unidentifiable, can only be judged on a case by case basis.

2.2 Knowledge in people

Information systems for medical and healthcare research act as intermediaries, not only for content brokerage, exploration and analysis, but also to provide a space for networking and collaboration among stakeholders. Knowledge creation is a collaborative process. New knowledge is produced through the interactions amongst people, rather than by an individual operating alone. Expert groups convene to design the research approach, to discuss and agree on research protocols, to assess the findings of the analysis and produce insights. To capitalise on the knowledge in a working group or in an organisation unit, processes and tools must exist for effective knowledge sharing and transfers: it is essential to build and maintain places of exchange and interaction and support them with the appropriate tools: networking and community building activities and application to support socialisation; reflective thinking tools to facilitate internalisation of concepts; discussion support tools to articulate and crystallise tacit knowledge in the form of explicit knowledge; and IT tools to convert explicit knowledge into more complex and systematic sets of explicit knowledge (Pappa et al., 2009).

Knowledge creation is not solely about information and how it is handled, but also about people and how they communicate. An information-value chain raises many moral and ethical issues that relate to both types of knowledge assets. Setting ethical codes to ensure the ethical function of the community or of the stakeholder teams formed around the processing of data is imperative. This involves setting out the values that underpin the stakeholders’ rights and obligations, creating rules and providing guidance on ethical standards and how to achieve them (compliance). Professional codes of practice that regulate specific professions need also to be respected. The investigation needs to consider the codes of conduct of the organisations individuals pertain to, i.e. the organisational values and principles, and the resulting directives for professional conduct.
The research field of **Computer-Supported Cooperative Work** (CSCW) is concerned with understanding social interaction and the design, development, and evaluation of technical systems supporting social interaction in teams and communities – or in other words it is about researching the use of computer-based technology for supporting collaboration. (Koch & Gross, 2006). The design work needs to specifically accommodate provisions for addressing threats to ethical behaviour in the work group: provisions for vertical support (top-down implementation and enforcement of consistent ethical behaviour standards) and for horizontal support (peer-to-peer ethical behaviour guidelines and enforcement tools).

### 2.3 Conclusion

With technology charting new grounds in research, many moral and ethical issues are raised across the information-value chains that typically relate to privacy protection and confidentiality, informed consent, transparency of management of the collected data, delegation of control, assurance mechanisms etc. Transformation increases complexity and creates challenges with regards to the data supply chain, collaboration, interconnectivity, that go beyond semantic and technical interoperability to the ethical congruence of systems and methods, which calls in addition for legal and organisational interoperability. The effects of digital content misuse can be severe. Therefore, instead of identifying and fixing ethical problems as they arise, a proactive approach is needed, including a thorough planning of measures based on an in-depth investigation of potential ethical risks. A clear definition of access and usage rights is needed. Data custodians have to have concrete information management plans to manage rights holder’s relationships, ensure the privacy of personal information, enforce accountability etc. Security infrastructures need to be put in place, in order to control the movement of digital information within and outside the user domain (access control) and protect content from unauthorised distribution and usage (usage control). Discussing Digital Rights Management, Pappa and Gortzis (2008) argued that DRM-conscious system and service design implies having a clear understanding of the technology requirements, solutions, and obstacles for any given application scenario. Central to DRM measures and solutions are the topics of privacy, policy, security, trust management, risk management, protection mechanisms, and information representation semantics. These solutions should guarantee security, privacy, safety, and quality of data and processes throughout the entire lifecycle of content, including both the communication and the application phase.
In a similar way, pharmacovigilance brings together stakeholders operating under different governance provisions (different legal structures etc). Data exchange rules and governance systems linked together as part of a specific organisational environment need to be interoperable and provide a guaranteed end-to-end quality-of-service. Establishing standards-based infrastructures emerges as an imperative requirement. Ideally, data governance provisions should be flexible and seamless (i.e. entirely transparent to the users of this data). In addition, since organisations go through constant changes, which often largely affect their knowledge-assets (more specifically the physical artefacts, in which the information is embedded, as well as the acquisition, management, processing and distribution of critical knowledge across the community of stakeholders), it is imperative for solutions to be flexible and allow for continuous improvement. In order to be effective, measures should be able to support organisational change and adjust to a changing operations scenario, recognising and adapting to opportunities and/or potential threats as they emerge.
Chapter 3: Methodology of Research

1. Introduction

The purpose of this chapter is to introduce the research methodology adopted for the present study, namely, to specify the research philosophy of this research study and to explain in detail the research strategy and the principal research methods applied. Durrheim (2006) describes research design as a “strategic framework”, a “plan” that guides research activity to ensure that sound conclusions are reached. According to Crotty (1998), at the starting point of research the following aspects need to be considered in sequence: the epistemology of the study, its theoretical perspective, methodology of research and choice of research methods. Similarly, Saunders et al. (2009) developed the research onion model (Figure 6), further detailing the consecutive stages that should be covered when designing a research methodology. According to Saunders et al. (2009) the process of designing a research methodology starts with the definition of the research philosophy (stage 1), and is followed by the identification of the appropriate research approach (stage 2) and the selection of a relevant research strategy (stage 3), the definition of the time horizon, in which to conduct the study (stage 4), and the data collection methodology to be applied (stage 5).

![Figure 6. The research “onion” (source: Saunders et al. (2009))](image-url)
Saunders et al. (2009) define methodology as “the theory of how research should be undertaken, including the theoretical and philosophical assumptions upon which research is based and the implications of these for the method or methods adopted”, and methods as “the techniques and procedures used to obtain and analyse research data, including for example questionnaires, observation, interviews, and statistical and non-statistical techniques”. Research methodology is concerned with the selection of an approach to the study that can address the targeted research question(s). The research questions one aims to answer and the respective research objectives constitute the purpose of the research project. Research projects are often classified according to their research purpose as exploratory, descriptive, explanatory. However, the research project may have more than one purpose (Saunders et al., 2009). Exploratory investigations aim to discover “what is happening; to seek new insights; to ask questions and to assess phenomena in a new light” (Robson, 2002). Explanatory studies focus on studying a situation or a problem in order to explain the relationships between variables (Saunders et al., 2009). Descriptive investigations revolve around portraying an accurate and exact profile of people, events or situations (Robson, 2002). Research strategy is described as the general plan of how the researcher will go about answering the research question(s), which, in turn, is/are shaped by the choice of research paradigm at the start of the research process. In the present case, the adopted theoretical perspective is of an interpretive nature. These issues will be addressed in the following sections.

The first part of the chapter outlines the philosophical foundations of the present research. Following a brief introduction to the concept of research philosophy and the principal research traditions (Section 2.1), the philosophical underpinnings of the present research are discussed (Section 2.2). A range of approaches were considered and choices were made according to the aims and context of the present research. Section 2.2 presents the research paradigm that informed the design of this research work, and analyses the reasons behind the philosophical classification of the study. The choice of research philosophy constitutes an epistemological and methodological frame of reference that defines the attitude and relation of the researcher to the production of data, and has strong implications on the research strategy in general and the choice of research tools and methods in particular. In the second part of the chapter the application of this entire framework to practice and the operationalisation of research is discussed. Section 3.4
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delves into questions of research strategy and research methods, as viewed through the lens of the research philosophy selected for the present study. Section XXX explains the choice of research approach and presents the research design. Subsequently, the tools and methods for the collection and analysis of primary data are presented and discussed. The section outlines the characteristics of these methods, presents their main advantages and disadvantages, and particularly discusses their ability to produce valid results in the present context, in order to meet the aims and objectives of the research. The section concludes with a brief discussion on the ethical considerations and limitations posed by the research methodology, as well as problems encountered during the research.

2. Research philosophy
2.1 The philosophical foundations of research
Research is a quest for developing knowledge in a particular field. Bryman et al. (2011) describe research as “the systematic investigation of a particular phenomenon in order to develop or increase knowledge of that phenomenon”. Overall, varying views exist about the appropriate course of knowledge seeking, although scholars agree that research should follow a systematic and methodical process of inquiry (Glaser & Strauss, 1967; Burrell & Morgan, 1997; Patterson & Williams, 1998; Saunders et al., 2009; Mertens, 2014). The way research is conducted is influenced by the researcher’s ‘worldview’ (Mackenzie & Knipe, 2006), perspective, or thinking, i.e. their set of beliefs that influence what should be studied, guide the research methods, inform the interpretation of research data and also relate to the kind of knowledge that is developed. Every research process is based on concrete philosophical assumptions about the way in which the researcher views the world: the nature of the world, the nature of knowledge, what constitutes ‘valid’ research, and which research methods are appropriate for the development of knowledge. In 1962, Thomas Kuhn introduced the term “research paradigm” to describe “the set of common beliefs and agreements shared between scientists about how problems should be understood and addressed” (Kuhn, 1962). Kuhn challenged the existence of a universal research paradigm, arguing that, in the long run, science experiences “paradigm shifts”, as established paradigms become discredited and become replaced by new ones that relate better to the actual concerns of practicing scientists (Blanche et al. 2006). A research paradigm represents the researcher’s “philosophical orientation” (Mertens, 2014), which is
guided by "a set of beliefs and feelings about the world and how it should be understood and studied" (Guba, 1990) and constitutes an “interpretative framework” (Guba & Lincoln, 1994), i.e. a “framework of understanding, through which theoretical explanations are formed” (Trochim & Donnelly, 2006). According to Guba and Lincoln (1994) a paradigm represents a “basic belief system (or metaphysics)” or “worldview” that guides the investigation and has significant implications for every decision made in the research process. A scientific paradigm is a whole system of thinking (Neuman, 2014) that sets the boundaries of research: what it is about and what is considered legitimate inquiry (Guba & Lincoln (1994).

2.1.1 Philosophical assumptions

Guba and Lincoln’s notion of paradigm builds on four major types of assumptions: ontological, epistemological, methodological and axiological (Guba & Lincoln, 1994; Lincoln & Guba (1985); Lincoln & Guba, 2000). Guba (1990) claims that answers to questions regarding these elements represent the “starting points or givens that determine what inquiry is and how it is to be practiced”. These assumptions provide an interpretive framework that guides the entire research process including strategies, methods, and analysis. Similarly, and despite omitting the element of axiology, Blanche and Durrheim (2006) describe a research paradigm as “an all-encompassing system of interrelated practice and thinking” that defines the nature of inquiry along the ontological, epistemological and methodological dimensions. Discussing research in the field of social science, Burrell and Morgan (1997) add another set of assumptions concerning “human nature”, which describe the relationship between human beings and their environment. In their discussion of beliefs that underlie the conduct of research, Orlikowski and Baroudi (1991) stress that researchers should also be concerned with the “relationship between theory and practice”, i.e with the purpose of knowledge in practice. Guba and Lincoln (1994) argue that questions of research methods are of secondary importance to questions of which paradigm is applicable to a given research. Most scholars agree that a top-down relation exists among the different categories of assumptions: the ontological assumptions made by the researcher will subsequently condition their epistemological view, and affect the choice of methodology, which will ultimately determine the methods employed for data collection and analysis (Hitchcock & Huges, 1995; Guba, 1990; Guba & Lincoln, 1994; Burrell & Morgan, 1997).

Ontology is concerned with “what is”, i.e. with the “nature of reality and its characteristics” (Creswell, 2007), or with the “essence of the phenomena being investigated” (Burrell & Morgan,
Ontological assumptions respond to the question “what is there that can be known?” (Guba & Lincoln, 1989:83), “what is the nature of reality?” or “What is the nature of the knowable?” (Guba, 1990). More specifically, ontology is concerned with whether reality is “given”, “external to individuals”, “imposed on the individual's’ consciousness”, and “of an objective nature”, or “the result of individual cognition” (Cohen et al., 2002). Reality can be regarded through different lenses, with views ranging from realism to critical realism to relativism. The Stanford Encyclopedia of Philosophy (Baghramian & Carter, 2017) describes relativism as “the view that truth and falsity, right and wrong, standards of reasoning, and procedures of justification are products of differing conventions and frameworks of assessment and that their authority is confined to the context giving rise to them”. In social science, ontology relates to assumptions about the nature of the social world and what can be known about it (Snape & Spencer, 2003). Burrell and Morgan (1997) identified two ways of conceiving social reality: the subjective and objective way. The objectivist approach to social science is characterised by a realist ontology, while the subjectivist by a nominalist ontology. The former assumes an “objective” view of social entities, as having a “reality that is external to social actors”. The later regards social entities as “social constructions, build up from the perceptions of social actors” (Bryman & Bell, 2015). Bryman and Bell (2015) employ the term ‘social ontology’ to discuss the nature of social entities and distinguish between two main ontological views of reality: objectivism and constructionism.

Epistemology is concerned with “how we come to know”, i.e. with the nature, forms and justification of human knowledge (Hofer & Pintrich, 1997; Crotty, 1998; Cohen et al., 2002). Mastin (2017) defines epistemology as “the study of the nature and scope of knowledge and justified belief”. It is also described as “a way of looking at the world and making sense of it” (Crotty, 1998) and a “study of how we know things” (Bernard, 2000), since it closely relates to the researcher's perceived relationship with the the known (or knowable), i.e. with knowledge they are un/dis/covering (Guba, 1990; Creswell, 2007). According to Burrell and Morgan (1997), epistemology refers to the “grounds of knowledge”, namely, to what it means to know, or “how one might begin to understand the world and communicate this as knowledge to fellow human beings”, and essentially dictates what is regarded as acceptable knowledge (Bryman & Bell, 2015). Epistemological assumptions are thus concerned with the nature, sources, and processes
of knowledge (Denzin & Lincoln, 1994; Gall, Borg, & Gall, 1996; Hofer & Pintrich, 1997; Snape & Spencer, 2003; Teddlie & Tashakkori, 2009). Two broad epistemological positions exist: positivism and interpretivism/constructivism, which view knowledge, as being either “hard, objective and tangible” or “personal, subjective and unique” (Cohen et al. (2002). The positivist view of knowledge is governed by the laws of nature, and calls for researchers to assume an observer role (objective/positive epistemology), while the later views knowledge as something interpreted by individuals, and imposes on researchers an involvement with their subjects (subjective/interpretive epistemology).

Methodology is concerned with the practical ways by which we come to know. According to Crotty (1998), methodology is the strategy or plan of action that lies behind the choice and use of particular methods, i.e. it represents the “general logic and theoretical perspective” of the inquiry (Bogdan & Biklen, 2007). It refers to the methods and procedures used in the research process (Creswell, 2014) and comprises the definition of tools and techniques of research (Neuman, 2000), namely, the research design, methods, approaches and procedures to be used in the investigation (Keeves, 1988). Methodology guides the selection of methods, namely the specific techniques and procedures used to collect, analyse and interpret data (Crotty, 1998; Bogdan & Biklen, 2007). Research methodology responds to the question “what is the process of research” (Creswell, 2007), “how should the inquirer go about finding out knowledge?” (Guba, 1990), “how can the inquirer go about finding out whatever they believe can be known? (Guba & Lincoln, 1994), “how do we know the world, or gain knowledge of it?” The methodology of research embodies philosophical assumptions, as it rests on a foundation of ontological and epistemological assumptions (Burrell & Morgan, 1997; Neuman, 2014). Methodology is closely related to epistemology, referring to the practice of knowing and the philosophy of how we come to know the world respectively. Overall, the researcher’s ontological view on the field of study frames their epistemological interaction with what they are researching, and determines the methodologies employed (Vasilachis, 2009). In social sciences, human nature assumptions also have direct implications of a methodological nature (Burrell & Morgan, 1997). According to Burrell and Morgan (1997), an objective view of social reality would point towards a nomothetic methodology, while a subjective consideration would lead to an idiographic approach. The nomothetic approach is about attempting to establish general rules, laws and generalisations, while idiographic research focuses on the study of the individual. Cohen et al.
(2002) make a distinction among scientific and positivist, naturalistic and interpretive, and mixed methodologies. Figure 7 summarises the positions of the two contrasting perspectives for conceiving social reality (objectivist and subjectivist), with regards to the ontological, epistemological, human and methodological assumptions, as illustrated by Burrell and Morgan (1997).

![Figure 7. Objectivist vs. subjectivist approach to social science [source: Burrell and Morgan (1997)]](image)

**Axiology** is a term used to refer to the branch of philosophy that deals with ethics, aesthetics, and religion (Lincoln & Guba, 2000). In research it is concerned with the role of values and ethics within the research process (Lincoln & Guba, 1985; Saunders et al., 2009). Values feed into all aspects of the inquiry process: from the choice of the problem, to the choice of research paradigm and the planning of the research methodology, to the presentation of the outcomes (Lincoln & Guba, 1985). Consequently, the researcher’s personal values may influence the credibility of the research results (Saunders et al., 2009). Assuming an objectivist approach to social science implies a value-free axiology, or axiological detachment, i.e. that the researcher’s personal values are excluded and have no influence on the research process (Lincoln & Guba, 2000; Saunders et al. (2009). Contrarily, a subjectivist approach acknowledges a value-bound, reflexive axiology, meaning that the researcher is part of what is being researched, and their personal values have a formative effect on the research process (Lincoln & Guba, 2000; Saunders et al. (2009).

### 2.1.2 Research paradigms

In research literature, a large number of paradigms have been proposed by scholars, offering a variety of views about the nature of the world (Guba, 1990; Guba & Lincoln, 1994; Hassard, 1995, Mertens, 2005; Rynes & Gephart, 2004; Mackenzie & Knipe, 2006, Willis, 2007). The
different paradigms, or “research traditions” (Couch, 1987; Rynes & Gephart, 2004), or “approaches” to science (Neumann, 2014), inherently contain distinctively different ontological and epistemological views that accordingly shape, constrain, and enable all aspects of inquiry (Paul & Elder, 1997). The exact number of paradigms and the names associated with each one vary from author to author. Candy (1989) proposed the categorisation of research paradigms into three main taxonomies: positivist, interpretivist, and critical paradigms. Guba (1990), and Guba and Lincoln (1994) identified four basic research paradigms: positivism (or empiricism), postpositivism (or postempiricism), constructivism, and critical theory. Smith (1993) discussed four alternatives: empiricism, postempiricism, critical theory, and interpretivism. In the field of social sciences, Willis (2007) named postpositivism, critical theory, and interpretivism, as the principal research paradigms. More recently, scholars proposed the addition a fourth category: the pragmatic paradigm (Tashakkori & Teddlie, 2003; Morgan, 2007). A study by Alise and Teddlie (2010) of the most popular methodological approaches across the social/behavioural sciences identified the following paradigms: postpositivism, constructivism, critical theory, transformative and pragmatism.

**Positivism**

Positivism builds on a realistic ontological position (naive realism), a positivist epistemology and the use of nomothetic methodologies (Burrell & Morgan, 1997). Positivists believe in empiricism, observation, experimentation and measurement (Guba, 1990; Cohen et al., 2002), stating that scientific method, with the use of structured instrumentation, is the primary or only way of discovering truths about the world (Orlikowski & Baroudi, 1991; Willis, 2007). As summarised by Cohen et al. (2002), positivists strive for “objectivity, measurability, predictability, controllability, patterning, the construction of laws and rules of behaviour, and the ascription of causality”. They consider science as “an attempt to gain predictive and explanatory knowledge of the external world” (Keat & Urry, 1975) and regard the outcomes of research as “objective facts and established truths” (Crotty, 1998). According to Orlikowski and Baroudi (1991), positivist research is premised on the existence of “a priori fixed relationships within phenomena”. Positivists claim that objects exist independent of the knower and can be objectively investigated by employing valid and reliable measurements. As a result, for the positivist new ideas can be accepted as knowledge only “if they can be put to the test of empirical experience” (Gray, 2014). Hesse (1980) claims that the basic posture of positivism is
both reductionist and deterministic. Historically, positivism represents the dominant approach of the natural sciences (Guba & Lincoln, 1994; Neuman, 2014; Gray, 2014). Positivism, acknowledges the existence of “only one logic” of science, to which any intellectual activity aspiring to the title of ‘science’ must conform” (Keat & Urry, 1975). Neuman (2014) notes that this approach entails the assumption that “eventually all science will become like the most advanced science, physics”, attributing any differences between the natural sciences and the other disciplines to the immaturity of the latter and their subject matter. Positivism has received strong criticism, being even characterised as “one of the heroic failures of modern philosophy” (Williams & May, 1996). Its relevance to the study of social phenomena and human behaviour has been particularly challenged (Keat & Urry, 1975; Cohen et al., 2002; Gray, 2014).

**Postpositivism**

The postpositive paradigm has emerged in an effort to respond to criticism to positivism, while maintaining the same set of core beliefs (Guba & Lincoln, 1994; Creswell, 2009). Postpositivism assumes a “critical realist” ontology, claiming that reality cannot be known by humans deterministically (Guba, 1990), but only apprehended “imperfectly and probabilistically” (Guba & Lincoln, 1994). Guba and Lincoln (1994) note that, epistemologically, postpositivists assume a modified dualist/objectivist position, claiming that it is possible to approximate (but never fully know) reality. In this light, they propose “critical multiplism” or triangulation methodologies, as a way to falsify hypotheses. Triangulation involves comparing outcomes that stem from a number of different data sources and methods to confirm findings.

**Interpretivism**

The interpretivist paradigm, often described as a “response to objectivism” (Willis, 2007), is characterised by an anti-positivist orientation, moving from an ontology of realism to an ontology of relativism (Guba, 1990; Willis, 2007). Relativism claims that reality exists in “multiple mental constructions, socially and experientially based, local and specific in nature” (Guba, 1990; Guba & Lincoln, 1994), meaning that reality is “subjective”, and that a person’s “perception of reality” is conditioned by their experiences and culture (Creswell, 2014). Interpretive research focuses on meanings and interpretations (Orlikowski & Baroudi, 1991). The central endeavour of the interpretivist is to “understand the subjective world of human experience” (Cohen et al., 2002) “in terms of its actors” (Cohen et al., 2002), namely, to study the individual’s interpretation of the world and assess the meanings that they assign to phenomena.
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Epistemologically, interpretivism takes a subjectivist position, which leads to the adoption of hermeneutic and dialectic research methodologies (Guba, 1990). Willis (2007) associates interpretivism with rationalism, as opposed to empiricism. The inquirer and the object of investigation are considered to be interactively linked, as new knowledge is created in interaction among investigator and respondents (Guba & Lincoln, 1994). Theory is thus viewed as “emergent”, not preceding research but arising from particular situations (Cohen et al., 2002). This paradigm is particularly resonant in the field of social science.

Critical Theory

Gray (2008) characterises critical research as a “meta-process of investigation”. While interpretivists adopt an uncritical stance towards the culture they are exploring, critical inquiry believes in the value-determined nature of inquiry. Guba (1990) employed the term ideologically oriented inquiry because a major focus of the critical approach is the analysis of data through the lens of an ideology. Orlikowski and Baroudi (1991) claim that aim of critical studies is to critique the status quo, “through the exposure of what are believed to be deep-seated, structural contradictions within social systems, and thereby to transform these alienating and restrictive social conditions“. Critical research “questions currently held values and assumptions and challenges conventional social structures” Gray (2008).

Table 13 presents the major research paradigms and summarises the principal ontological and epistemological assumptions, beliefs, norms and values that each paradigm holds.

<table>
<thead>
<tr>
<th>Item</th>
<th>Positivism</th>
<th>Postpositivism</th>
<th>Critical Theory et al.</th>
<th>Construtivism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ontology</td>
<td>Naïve realism – “real” reality but apprehendable</td>
<td>Critical realism–“real” reality but only imperfectly and probabilistically apprehendable</td>
<td>Historical realism–virtual reality shaped by social, political, cultural, economic, ethnic, and gender values; crystallized over time</td>
<td>Relativism –local specific constructed realities</td>
</tr>
<tr>
<td>Epistemology</td>
<td>Dualist/objectivist; Finding truth</td>
<td>Modified dualist/objectivist; critical tradition/community; findings probably true</td>
<td>Transactional/subjectivist; value mediated findings</td>
<td>Transactional/subjectivist; created findings</td>
</tr>
<tr>
<td>Methodology</td>
<td>Experimental/manipulative; Verification of hypotheses; chiefly quantitative methods</td>
<td>Modified experimental/manipulative; critical multiplicism; falsification of hypotheses; may include qualitative methods</td>
<td>Dialogic/dialectical</td>
<td>Hermeneutical/dialectical</td>
</tr>
</tbody>
</table>
Chapter 3: Methodology of Research

The selection of paradigm has been the subject of long-standing debate in several disciplines (Couch, 1987; Tashakkori & Teddlie, 1998; Hall, 2013; Neuman, 2014). During the 1970s and 80s, these “paradigm wars” have caused fierce debates among supporters of the positivist/empiricist and the constructivist/phenomenological approach, over important conceptual issues such as the “nature of reality” or the “possibility of causal linkages” (Tashakkori & Teddlie, 1998). More recently, scholars have begun to challenge the existence of a “prevalent research paradigm” that represents the “right” positions to be adopted by scholars in a particular discipline in order to develop a better understanding of the research questions at hand and shape their research process accordingly. Researchers realised that there was no necessary antagonism between the different schools of thought, that research approaches were not necessarily mutually exclusive (e.g. quantitative and qualitative methods), but were merely addressing different important topics (Tashakkori & Teddlie, 1998). Hall (2013) notes that, following the “paradigm wars” new approaches emerged, leading to three basic categories of research: (a) a-paradigmatic research, ignoring paradigmatic issues altogether; (b) multiple paradigm research, accepting the existence of alternative paradigms; and (c) single paradigm research, accommodating quantitative and qualitative research under a single paradigm. Tashakkori and Teddlie (1998) note a tendency towards “paradigm relativism”, which recommends the use of whatever philosophical and methodological approach is more appropriate for the particular research problem under study. On the subject, Creswell (2009) writes that it is possible that one paradigm (like pragmatism) may serve as an adequate foundation for “concurrent or parallel types of designs”, while paradigms may “shift” during a sequential design. Tashakkori and Teddlie (1998) claim that it is more appropriate in a particular study to view research philosophy as a “continuum” rather than opposite positions. Patterson and Williams described science as a pluralistic “collection of paradigms” (Patterson, 2000). They defined science as “a systematic set of empirical activities for constructing, representing, and analysing knowledge about phenomena being studied”...”which is guided by a set of normative philosophical commitments shared by a community of scholars” (Patterson & Williams, 1998). Patterson and Williams (1998) developed a three-level, hierarchical model of the macrostructure of scientific research, consisting of: (i) top-level “worldviews” that focus on the definition of science (i.e. broad philosophical debates concerning the nature of science and the concept of validity); (ii) mid-level “paradigms” that focus on the practice of science (i.e. debates
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concerning the normative philosophical commitments underlying specific approaches to science); and (iii) low-level "research programs" that focus on the application of science (i.e. specific empirically centered debates concerning theory and the specific methods of collecting, analysing, and interpreting data).

**Pragmatism**

According to Saunders et al. (2009) the pragmatist ontology, epistemology and axiology are focused on improving practice. Pragmatism emphasises practical outcomes (Creswell, 2007; Saunders et al., 2009; Biesta, 2010), highlighting workable approaches to problem solving (Morgan, 2014). The research problem and the research question represent the most important determinants for research design and strategy (Tashakkori & Teddlie, 2003; Creswell, 2007). According to Morgan (2007), pragmatism emphasises abduction, intersubjectivity, and transferability, connecting induction with deduction, subjectivities and objectivity, context and generality. For this reason, pragmatism is regarded as an effective alternative to traditional paradigms that offers a range of new opportunities (Morgan, 2007). Pragmatists can adopt a wide range of research strategies, the choice of which is driven by the specific nature of the research problems. Pragmatism is frequent associated with Mixed-Methods Research (MMR), but can also employ qualitative or quantitative methods (Morgan, 2014). Nonetheless, the value of pragmatism as a philosophy for social research goes beyond methodological practicality (Morgan, 2014). Denzin (2012) describes pragmatism as “a doctrine of meaning, a theory of truth”, which claims that “the meaning of an event cannot be given in advance of experience”. The researcher assumes the role of the interpreter, who “examines and inspects, and reflects on an action and its consequences” (Denzin, 2012). According to Denzin (2012) neo-pragmatists endorse a “thoroughly interpretive, hermeneutic pragmatism that is explicitly antipositivist, antifoundational, and radically contextual”. Morgan (2007) notes that pragmatism places its emphasis on “shared meanings and joint action”, namely, on actual behaviour (“lines of action”), on the beliefs that support those behaviours (“warranted assertions”), and on the consequences that are likely to follow from different behaviours (“workability”).
2.2 The philosophical underpinnings of the present research

This section discusses the philosophical assumptions that underpin this research and presents the rationale underlying the choice of approach. Overall, the research philosophy one adopts contains important assumptions about the nature of research. The ontological and epistemological decisions made, frame the researcher’s thinking about a given research problem, and how they might approach it, in order to answer the research question at hand. Choices made will underpin the research strategy and the methods to be used as part of that strategy. With a vast diversity of research approaches proposed in literature, it would be easy to fall into the trap of a “paradigm war”-type debate, and search for the universally “best” research paradigm, thinking that one research philosophy is ‘better’ than another. In reality, the “value” of research paradigms depends on their application, with each paradigm being “better” at doing different things. There cannot exist an “absolute best” research paradigm. As discussed in Section 3.2, scholars are increasingly challenging the existence of a “correct”, universal research paradigm within a single discipline. The notion of necessary antagonism or incompatibility between paradigms is deemed unjustified. Instead, the best way forward depends on the unique context of each research: the choice of the “correct” or “best” research paradigm depends on the research question(s) one is seeking to answer. Central to the selection process is the dichotomy between positivism and idealism, without being the sole criterion.

2.2.1 Context of the present research

Research is a systematic investigation, seeking to find answers to a problem. Applied research, in particular, is concerned with solving practical problems of the modern world, rather than with acquiring knowledge for the sole purpose of knowledge acquisition. This is the case of the present inquiry in the field of pharmacovigilance. The present research is a knowledge development process, situated in the social-scientific domain. Work falls in the area of Information Science (IS) and Management Research, while it also relates to Life Sciences, targeting an identified gap between IS research and its application in pharmacovigilance. Objective of the present research is to develop a Reference Framework for collaborative, information-driven innovation in the field of pharmacovigilance that can be used to describe and assess the implementation of pharma safety investigations, as well as to guide and educate stakeholders towards the design, optimisation and innovation of pharmacovigilance implementations. The inquiry can, therefore, be characterised as context-driven, problem-
focused and interdisciplinary. Overall, this research draws from science and technology, as well as social sciences and the humanities.

**Social science**

Historically, the methodological unity of natural and social science has been challenged (Keat & Urry, 1975), with several scholars arguing in favor of the adoption of the interpretive paradigm in social sciences research (Burrell & Morgan, 1997). In the 18th century, Dilthey stated that Verstehen (understanding) was the goal of social science research and that the proper topic of social science research was the lived experiences of humans []. Presently, the broader area of social science research is divided between two competing methods: the scientific empirical tradition, and the naturalistic (or interpretive) phenomenological mode (Burns, 2000). The former has a nomothetic orientation, while the latter focuses on the individual case and is characterised as ideographic. There exist three major approaches to social research: (a) **Positivist social science** (PSS) that emphasises discovering causal laws, careful empirical observations, and value-free research; (b) **Interpretative social science** (ISS) that emphasises meaningful social action, socially constructed meaning, and value relativism; and (c) **Critical social science** (CSS) that emphasises combating surface-level distortions, multiple levels of reality, and value-based activism for human empowerment.

**Information Science**

Information Science is positioned “at the confluence of people, organisations and technology” (Hevner et al, 2004). Wersig (1993) argues that “social organisations and technological systems always have been grown within society as solutions to needs felt to be solved”. Consequently, the ongoing relations among information technology, individuals, and organisations constitute a primary concern of information systems research (Orlikowski & Baroudi, 1991). Galliers (1990) categorised information science as either **empirical** or **interpretative**. While discovering that much information systems research reflects a positivistic orientation, Orlikowski & Baroudi (1991) advocated considering a plurality of research perspectives for the investigation of information systems phenomena, as each approach can provide new insights on the relationships between information technology, people, and organisations. According to Walsham (1993), the use of interpretive research methods in the study of information systems would allow researchers to develop “an understanding of the context of the information system, and the process whereby the information system influences and is influenced by the context”.

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Business and management research

Business and management research is not a single pure academic discipline (e.g. like chemistry) (Myers, 2013). Bryman and Bell (2015) have employed the term “business research” to refer to academic research on topics relating to questions that are relevant to the field of business and management and have a social science orientation. Zikmund et al. (2013) defined business research as “the application of the scientific method in searching for the truth about business phenomena”. Business research can be described as “a systematic and organised effort to investigate a specific problem encountered in the work setting that needs a solution” (Sekaran, 2000). Business is an umbrella term involving a number of different academic disciplines. Saunders et al. (2009) argue that business and management research is transdisciplinary, and engages with both theory and practice. They stress that “all business and management research projects can be placed on a basic–applied continuum according to their purpose and context”.

Van de Ven and Johnson (2006) examine three ways in which the gap between theory and practice has been framed: as a knowledge transfer problem, as concerning two distinct kinds of knowledge, and as a knowledge production problem. Discussing the nature and purpose of management research, MacLean et al. (2002) argue that mode 2 knowledge production (Gibbons et al., 1994) has become increasingly prominent in the field. Mode 2 views knowledge as the result of a broader range of considerations (Gibbons et al., 1994). MacLean et al. (2002) summarised its main attributes as follows: “Knowledge produced in the context of application”, “Transdisciplinarity”, “Heterogeneity and organisational diversity”, “Social accountability and reflexivity”, and “Diverse range of quality controls”. In their study of organisation theory, Tsoukas & Knudsen (2003) concluded that several "schools of thought" exist in business and management, with scholars challenging the dominance of "scientific rationality" in organisation studies. Saunders et al. (2009) explain that ontologically the social phenomenon of management can be researched either in an objectivist way, emphasising the structural aspects of management and assuming that management is similar in all organisations, or in a subjectivist way claiming that managers attach their own individual meanings to their jobs. Burrell and Morgan (1982) proposed the categorisation of social science paradigms that can be used in management and business research, into four categories: functionalist, interpretive, radical humanist, and radical structuralist. Saunders et al. (2009) identified five major philosophies in business and management: positivism, critical realism, interpretivism, postmodernism and pragmatism.
Chapter 3: Methodology of Research

The main attributes and the most popular research methods associated with these research philosophies are summarised in Table 14.

**Table 14. Characteristics of research philosophies in business and management studies**

[source: Saunders et al. (2009)]

<table>
<thead>
<tr>
<th>Philosophy</th>
<th>Ontology</th>
<th>Epistemology</th>
<th>Axiology</th>
<th>Typical methods</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positivism</strong></td>
<td>Real, external, independent</td>
<td>Scientific method</td>
<td>Value-free research</td>
<td>Typically deductive, highly structured, large samples, measurement, typically quantitative methods of analysis, but a range of data can be analysed</td>
</tr>
<tr>
<td></td>
<td>One true reality (universalism)</td>
<td>Observable and measurable facts</td>
<td>Researcher is detached, neutral and independent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Granular (things)</td>
<td>Law-like generalisations</td>
<td>of what is researched</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ordered</td>
<td>Numbers</td>
<td>Researcher maintains objective stance</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Causal explanation and prediction as</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>contribution</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Critical realism</strong></td>
<td>Stratified/layered (the empirical, the actual</td>
<td>Causal mechanisms</td>
<td>Value-laden research</td>
<td>Retroductive, in-depth historically situated analysis of pre-existing structures and emerging agency. Range of methods and data types to fit subject matter</td>
</tr>
<tr>
<td></td>
<td>and the real)</td>
<td>Epistemological relativism</td>
<td>Researcher acknowledges bias by world views,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>External, independent</td>
<td>Knowledge historically situated and transient</td>
<td>cultural experience and upbringing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intransient</td>
<td>Facts are social constructions</td>
<td>Researcher tries to minimise bias and errors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Objective structures</td>
<td>Historical causal explanation as contribution</td>
<td>Researcher is as objective as possible</td>
<td></td>
</tr>
<tr>
<td><strong>Interpretivism</strong></td>
<td>Complex, rich socially constructed through</td>
<td>Theories and concepts too simplistic</td>
<td>Value-bound research</td>
<td>Typically inductive. Small samples, in-depth investigations, qualitative methods of analysis, but a range of data can be interpreted</td>
</tr>
<tr>
<td></td>
<td>culture and language</td>
<td>Focus on narratives, stories, perceptions and</td>
<td>Researchers are part of what is researched,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple meanings, interpretations, realities</td>
<td>interpretations</td>
<td>subjective</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flux of processes, experiences, practices</td>
<td>New understandings and worldviews as</td>
<td>Researcher interpretations key to contribution</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>contribution</td>
<td>Researcher reflexive</td>
<td></td>
</tr>
<tr>
<td><strong>Postmodernism</strong></td>
<td>Nominal</td>
<td>What counts as ‘truth’ and ‘knowledge’ is</td>
<td>Value-constituted research</td>
<td>Typically deconstructive – reading texts and realities against themselves In-depth investigations of anomalies, silences and absences Range of data types, typically qualitative methods of analysis</td>
</tr>
<tr>
<td></td>
<td>Complex, rich</td>
<td>decided by dominant ideologies</td>
<td>Researcher and research embedded in power</td>
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<tr>
<td></td>
<td>Socially constructed through power relations</td>
<td>Focus on absences, silences and oppressed/</td>
<td>relations</td>
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<tr>
<td></td>
<td>Some meanings, interpretations, realities</td>
<td>repressed meanings, interpretations and voices</td>
<td>Some research narratives are repressed and</td>
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<td></td>
<td>are dominated and silenced by others</td>
<td>Exposure of power relations and challenge of</td>
<td>silenced at the expense of others</td>
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</tr>
<tr>
<td></td>
<td>Flux of processes, experiences, practices</td>
<td>dominant views as contribution</td>
<td>Researcher radically reflexive</td>
<td></td>
</tr>
<tr>
<td><strong>Pragmatism</strong></td>
<td>Complex, rich, external. ‘Reality’ is the</td>
<td>Practical meaning of knowledge in specific</td>
<td>Value-driven research</td>
<td>Following research problem and research question</td>
</tr>
<tr>
<td></td>
<td>practical consequence of ideas. Flux of</td>
<td>contexts</td>
<td>Research initiated and sustained by researcher’s</td>
<td>Range of methods: mixed, multiple, qualitative, quantitative, action research Emphasis on practical solutions and outcome</td>
</tr>
<tr>
<td></td>
<td>processes, experiences and practices</td>
<td>‘True’ theories and knowledge are those that</td>
<td>doubts and beliefs</td>
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<td>enable successful action. Focus on problems,</td>
<td>Researcher reflexive</td>
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<td>practices and relevance Problem solving and</td>
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<td>informed future practice as</td>
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2.2.2 Philosophical classifications of the present study

The selection of the “correct” research paradigm for the present research work was based on the criterion of suitability: the paradigm’s ability to (a) capture the essence of the phenomenon under study and (b) support the investigation of the research questions through appropriate research methods for data collection, analysis and interpretation. For the philosophical classification of the present study, different approaches were considered and choices were made according to the aims and context of the present research. The latest developments in the practice of research were considering, with emphasis on research philosophies applied in the field of business and management (Saunders et al., 2009; Bryman et al, 2011). This led to the identification of the following potential paradigms: positivism, critical realism, interpretivism, postmodernism and pragmatism. The subsequent examination of their attributes against the requirements of the present inquiry was concluded with the selection of the pragmatic paradigm. Were the inquiry focused on a specific aspect of pharmacovigilance, it is likely that a different research approach would apply. Following is an analysis of the principal reasons behind this choice of philosophical classification.

In the present research, the phenomenon under study is the advancing digitisation of pharmacovigilance, which is considered under a holistic and forward looking lense. The scope of this inquiry is essential, not phenomenological (Novikov & Novikov, 2013). The aim is to identify the internal sides, mechanisms and driving forces of technology-enhanced pharmacovigilance, rather than to merely describe its externally observed characteristics.

Considering the choice between nominalist (subjectivist) and realist (objectivist) ontology, which underpins the traditional dichotomy between positivist and interpretivist research philosophies, our investigation concluded that a realist ontology would not be appropriate, given the scope and nature of the present inquiry. The present research rejects the positivist idea of a single tangible reality that can be predicted and controlled, and the positivist notion of what constitutes knowledge, which builds on observation and empirical study. In the present case, while the foundation of the research work is empirical (investigation of existing and emerging practices, and their nuances), the constantly evolving nature and the increasingly social dimension of pharmacovigilance is recognised. It is not about discovering a unique truth, but about pharmacovigilance stakeholders creating their view of the world, i.e. being able to launch
research investigations that reflect their individual perspectives and needs. There cannot be a single reality, a single system specification. Instead, a framework is called for, in order to allow stakeholders to shape and combine available capabilities towards meaningful investigations, interpreting and matching their specific needs. The positivist paradigm would thus not be applicable, given its “single truth” ontological assumption, which leads to an explanatory and causal-factual and technocratic research outlook that searches for causality and fundamental laws. Overall, it can be concluded that the notions of objectivity, measurability, predictability, controllability, and irrefutable laws and rules, which underpin a positivist worldview (Cohen et al., 2002) do not apply in the present case. Similarly, for the present study the post-positive (critical realism) research paradigm should be rejected, given that critical realists also accept the existence of an “objective reality”, which exists independently of human thoughts and beliefs, despite advocating a relativist approach to epistemology. On the whole, the pharmacovigilance reality is too complex and multidimensional to be understood solely through the process of observation. Adopting a positivist stance would imply reducing this complexity to a series of law-like generalisations, and, as a result, the research would risk missing rich insights into this complex world. Explanation, description and interpretation are called for, in order to achieve deeper levels of knowledge. A comprehensive and contextual, rather than a reductionist and isolationist, research approach is more relevant to the present context.

This view of the field of pharmacovigilance largely coincides with the picture painted by Lincoln and Guba (1985) in their discussion of “naturalistic inquiry”: all entities under study are in a constant flux, in a state of mutual simultaneous shaping. Reality in the constantly evolving field of pharmacovigilance, is neither singular nor objective. In this field of study, multiple realities that change over time can be identified. Inquiry into these realities can only be naturalistic (Lincoln & Guba, 1985) aspiring to achieve some level of understanding (verstehen) of these realities as they emerge and take form through social conditioning (relativist ontology), and to produce a set of “working hypotheses” that provide the means to understand the field, i.e. to develop an idiographic, rather than a nomothetic, body of knowledge.

The interpretivist approach is characterised by a relativist ontology, and a subjectivist epistemology, which suggests that knowledge is socially constructed, and subjective. It implies the existence of relationship and interaction between the outcome of the inquiry and the research participants. Willis et al., 2007) note that interpretivists “generally take a nondeterministic view
of things and adopt instead the view that each person can determine his or her own behavior”. According to Burrell and Morgan (1979), interpretivism is suitable for capturing the rich complexity of social situations. They further note that, in principle, an interpretivist perspective is considered highly appropriate in the case of business and management research, particularly in such fields as organisational behaviour, marketing and human resource management. Several limitations to interpretive research exist, namely with regards to the subjective nature of this approach. Questions are raised about the generalisability of interpretivist research, which, however, some scholars regard as not of crucial importance in areas like business research, when studying the ever-changing world of business organisations (Burrell & Morgan, 1979). Neuman (2014) states that “social scientific evidence is contingent, context specific, and often requires bracketing”. The phenomenon under study in the present research shares the characteristics of business research. Each pharmacovigilance investigation is complex and unique, being a function of a particular set of circumstances and individuals. Generalisation, in its deterministic sense, is less valuable, as the circumstances of today may not apply in the future. Aim of the present research is to capture the rich complexity of the field, in order to create the means for future pharmacovigilance investigators to effectively navigate through it. Given the epistemological and methodological restrictions of the interpretivist paradigm, committing to a purely interpretative approach would risk being restrictive for the purposes of the present research, which is problem-driven, and, beyond developing an understanding of the domain, aspires to contribute practical solutions that can inform future practice. Aim of the research process is to develop a practical framework, to orchestrate the cooperative, bottom-up creation of knowledge in the area of medicines safety surveillance. The medicines safety innovation landscape is already showing signs of a gradual evolution into an ecosystem, shifting its methods, processes, cultural habits and competencies from episodic management of drug safety challenges to more holistic, continuum-oriented approaches. The complexity of the research area calls for a reflexive process of inquiry. Accepting as irrefutable truth for the present research the constructionist view that reality is socially created, and relying solely on ideographic explanations, would limit the perspective of the study. In this sense, the present inquiry is more aligned with the pragmatist view of research. Indeed, through revision of the individual attributes of the pragmatic paradigm, it was concluded that this paradigm represents the most relevant approach for dealing with the complexity of the research context and
addressing the research questions set in the present work. Pragmatists recognise that there are many different and not mutually exclusive ways of interpreting the world and undertaking research. In this light, they propose the integration of different perspectives, namely, that either or both observable phenomena and subjective meanings can provide acceptable knowledge. As a result, pragmatist research is characterised by considerable variation in terms of how ‘objectivist’ or ‘subjectivist’ its underlying assumptions are (Saunders et al., 2009).

While the present research leans towards interpretivist positions, a more pragmatic and flexible approach is needed. Adopting a strict interpretive position would be rather restrictive and could jeopardise the success of the research process. Noteworthy is Couch’s assertion, when discussing the future of the sociological enterprise under the objective-subjective epistemological dilemma, who claimed that “if sociology is to be transformed into a viable social enterprise that conducts research that will allow for the formulation of generic assertions about social life it will be necessary to formulate programs consistent with the epistemological position of the subjectivists that calls for the study of process, but accepts the epistemological implication of the objectivists’ position that calls for controlled observations” (Couch, 1987). In the present research, while the objective is to understand a phenomenon and to create knowledge in an interpretative way, through social constructions and experience (subjectivist position), relevant formal propositions and deductions (objectivist position) are investigated and taken into consideration as well. This is aligned with the pragmatists philosophy.

A further argument in favour of the adoption of a pragmatic approach is that pragmatism is interested in practical outcomes, rather than in abstract distinctions. This coincides with the main requirement set for the present research: a need to achieve both scientific rigour and relevance (Myers, 2013), namely, to ensure that scientific standards are met and that the research outcomes are of relevance to the application domain. The pragmatist research philosophy accepts concepts to be relevant only if they support action. Rather than examining the possibility or impossibility of generalisability, pragmatism introduced the concept of transferability, which focuses on what people can do with the knowledge they produce (Morgan, 2007; Plano Clark & Creswell, 2008). Pragmatism is based on the belief that theories can be both contextual and generalisable by analysing them for ‘transferability’ to another situation.

The present inquiry adopts a multi-perspective view on the phenomenon, placing incoming data and information under continuous scrutiny against the pragmatist principles of truth, reality and
relevance to practice. It recognises a dialogical aspect in the research process, also described by Klein and Myers (1999) in the context of interpretative research, as the “Principle of Dialogical Reasoning”. This implies a need for sensitivity to possible contradictions between the theoretical preconceptions that guide the research design and the actual findings.

The research philosophy one adopts involves important assumptions about the way in which they view the world and conditions the research strategy and the methods selected as part of that strategy. The pragmatist paradigm has a significant advantage with regards to the operationalisation of research, as its inherent mixed methods. Of particular relevance to the present research is the use of abduction in pragmatic reasoning as described by Plano Clark and Creswell (2008): implementing a process of inquiry that “evaluates the results of prior inductions through their ability to predict the workability of future lines of behaviour”. According to this approach, observations are first converted into theories and then these theories are assessed through action.

3. Research Hypotheses, Purpose and Objectives

An important step in the planning of research is to be clear about its purpose and scope. Commencing from the research opportunity identified (Chapter 1), the following research hypothesis, purpose and objectives are set.

3.1 Research hypotheses

A hypothesis can be described as a tentative answer to the research problem. It is a carefully constructed statement of prediction about the phenomenon under study that is testable and falsifiable (Popper, 1957). In the case of exploratory research, whose purpose is to develop knowledge and generate hypotheses about the phenomenon under study, the formulation of meaningful research hypotheses is questionable. The present study has a strong exploratory dimension. In the light of the above, the following three hypotheses are formulated based on inductive reasoning from prior observations, mainly to denote the purpose of research and the criteria of success.

Hypothesis 1

$H_1$: The development of a Reference Framework for collaborative, and information-driven pharmacovigilance is feasible.
The study will investigate the emerging landscape in pharmacovigilance, to explore how advanced digitisation technologies are revolutionising the field, pushing pharmacovigilance towards increasingly collaborative, and information-driven practices. It is possible to develop a Reference Framework (the Knowledge Discovery Cube Framework or KDC Framework) for collaborative, information-driven innovation in pharmacovigilance to comprehensively depict the emerging landscape amidst the proliferation of data and the growing digitisation: the processes of innovation, the actors, and their interrelationships.

**Hypothesis 2**

\[ H_2 : \text{The KDK Framework for collaborative, information-driven pharmacovigilance can deepen the collective understanding of how a principled, collaborative and balanced pharma safety data ecosystem can be organised and guide and educate stakeholders towards the optimisation of these services.} \]

The KDK Framework will allow stakeholders to seek and find affordances that need be mobilised in terms of resources, devices and systems by decontextualizing the objects of experience, reducing them to their useful properties and determining their interrelationships.

**Hypothesis 3**

\[ H_3 : \text{The KDK Framework for collaborative, information-driven pharmacovigilance can serve the purposes of continual analysis, providing a mechanism for shaping research and managing technology adoption in an informed and intentional manner.} \]

The KDK Framework can provide useful reference points for the ongoing research and development process in the field, in terms of both strategic planning and innovation adoption.

A fourth hypothesis can be formulated, underpinning the validation stage of the research work. The validation process can be viewed as a self-contained research project within the present inquiry, following the development of the Reference Framework. Validation is pursued via the operationalisation of the KDK Framework in the area of vaccine safety (Smart Investigation Environment).

**Hypothesis 4**
The research effort during the validation stage is directed towards rejecting or disproving the aforementioned statement, which relates to the generalisability of the KDK Framework. The investigation of $H_4$ represents a case of null hypothesis testing. This process makes use of deductive reasoning, in an effort to ensure that the truth of conclusions is irrefutable. In the present research, the validation process is an attempt to find practical evidence that could falsify the $H_4$ claim (by means of the ADVANCE case study, the revision of other sources etc). Failing to reject this hypothesis means that the alternative (null) hypothesis is false.

3.2 Research purpose

Advanced digitisation is transforming science and society, and reshaping the field of pharmacovigilance. The purpose of the present research is to explore the emerging landscape in pharmacovigilance and to develop a Reference Framework for collaborative, information-driven innovation in the field of pharmacovigilance that can be used to describe and assess the implementation of pharma safety investigations, as well as to guide and educate stakeholders towards the design, optimisation and innovation of pharmacovigilance implementations.

Against the backdrop of the medical/Drug data and technology revolution, the Knowledge Discovery Cube Framework represents a method for continual analysis, a mechanism for managing technology adoption in an informed and intentional manner. At any given instance, the Knowledge Discovery Cube Framework will help assess the existing conditions to identify the capabilities and risks of the process (Capability determination) to derive considerations and recommendations and develop opportunities for future improvement. In that sense, the Framework will support the implementation of any Evidence Creation Process: it will provide insight and reveal areas of potential improvement to be considered for the setup of the Evidence Creation Process.

The present research is not envisaged as a conceptual study, but rather as an empirical investigation that relies on empirical data and is informed by theory (Myers, 2013). Typically, research studies are classified according to their research purpose as: exploratory, descriptive or explanatory (Saunders et al., 2009). A research project may have more than one purpose. In
principle, the present research is of an exploratory nature, as it entails a search for new insights in the evolving domain of pharmacovigilance, in an effort to develop new, and relevant ways of looking at things, and to lay the foundations that will lead to future studies and eventually to the implementation of new pharmacovigilance methods. An exploratory research design is deemed most useful for inquiry projects that are addressing a subject about which high levels of uncertainty exist. In this light, the present study sets out to develop a new and comprehensive understanding of the topic, starting with a broad focus initially, which becomes progressively narrower as the inquiry advances. The inquiry proceeds in an explanatory direction, aiming to define and explain the relationships between the identified variables. This is pursued mainly by means of qualitative data collection and analysis.

3.3 Research objectives

Research objectives describe what one aims to achieve by a research project. In order to accomplish the research purpose of the present research, the following detailed objectives are set:

I. Exploration of the pharmacovigilance domain

O₁: Develop an in-depth understanding of pharmacovigilance investigations and the emerging evidence landscape and define concepts and paradigms relevant to this study.

H₁

II. Development of Reference Framework

O₂: Explore relevant models and theories in the field and beyond, and identify concepts and paradigms relevant to this study.

H₁

O₃: Define design requirements for a Reference Framework.

H₁

O₄: Develop the KDK Reference Framework on the basis of the identified requirements and learnings from relevant models and theories.

H₁

III. Empirical validation

O₅: Verify that the Reference Framework satisfies all the design requirements.

H₂-H₃

O₆: Operationalise and validate the Reference Framework in practice.

H₄

These detailed objectives correspond to different implementation phases of the research work and contribute to one or more of the research hypotheses formulated. Table 17 (Phases of Research) illustrates these interrelationships and also indicates the chapter in which each element is discussed.
Chapter 3: Methodology of Research

4. Operationalisation of research

Research is a systematic investigation that aims to generate knowledge about a particular phenomenon. The research strategy describes the tools and procedures used for collecting and analysing data to answer the research questions and ultimately to provide a solution to the research problem. It follows a concrete methodology of research that involves the use of relevant research methods, in line with the philosophical foundations and the objectives of the study. This section describes the main actions taken to investigate the current research problem, as described above, and the rationale for the application of specific procedures or techniques. The present inquiry is founded on the pragmatist philosophy, which accepts and recommends the use of any combination of methods, in order to find answers to research questions, namely both empirical-analytical and interpretative approaches. Similarly, in the present research, both inductive approaches (typically employed by interpretivists) and deductive approaches (typically employed by positivists) are employed for specific purposes, at different stages of the study process. The former focus on subjective knowledge and explanation, and are aimed at analysing the meaning-making practices of human subjects. The latter focus on objective knowledge, and employ deductive reasoning that uses existing theory as a foundation for formulating hypotheses that need to be tested. Section 4 discusses the theoretical foundations and the key parameters of the implementation of the research process and section 5 outlines the research plan adopted for the present research work.

4.1 Research approach

The main sources of human knowledge are: intuitive, authoritative, logical, and empirical knowledge (Slavin, 1984). Different ways of acquiring knowledge exist. People attempt to comprehend the world around them by using three types of reasoning or inference: deductive, inductive, and abductive, which employs a combination of the two (Cohen et al., 2002; Saunders et al., 2009). Collins and Hussey (2013) defined deductive research as “a study in which a conceptual and theoretical structure is developed and then tested by empirical observation; thus particular instances are deducted from general influences.” Deduction begins with hypotheses formulated on the basis of existing knowledge or literature (Burrell & Morgan, 1979; Silverman, 2013; Leedy & Ormrod, 2014). Deductive reasoning is a "top-down" method,
with emphasis placed mainly on the investigation of causality that seeks to test an established theory or a hypothesis, i.e. to confirm, refute or modify the investigated principle. These hypotheses present an assertion about two or more concepts that attempts to explain the relationship between them. Concepts represent abstract ideas that form the building blocks of hypotheses and theories. The first stage, therefore, is the elaboration of a set of principles or allied ideas that are subsequently tested through empirical observation or experimentation.

<table>
<thead>
<tr>
<th>Deduction emphasis</th>
<th>Induction emphasis</th>
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<tbody>
<tr>
<td>• scientific principles</td>
<td>• gaining an understanding of the meanings humans attach to events</td>
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<tr>
<td>• moving from theory to data</td>
<td>• a close understanding of the research context</td>
</tr>
<tr>
<td>• the need to explain causal relationships between variables</td>
<td>• the collection or qualitative data</td>
</tr>
<tr>
<td>• the collection or quantitative data</td>
<td>• a more flexible structure to permit changes of research emphasis as the research progresses</td>
</tr>
<tr>
<td>• the application of controls to ensure validity of data</td>
<td>• a realisation that the researcher is part of the research process</td>
</tr>
<tr>
<td>• the operationalisation of concepts to ensure clarity of definition</td>
<td>• less concern with the need to generalise</td>
</tr>
<tr>
<td>• a highly structured approach</td>
<td></td>
</tr>
<tr>
<td>• researcher independence of what is being researched</td>
<td></td>
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<tr>
<td>• the necessity to select samples of sufficient size in order to generalise conclusions</td>
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</tbody>
</table>

Figure 8. Comparison of deductive and inductive approaches to research [Source: Saunders et al. (2009), Burrell and Morgan (1979)]

Inductive research is defined as “a study in which theory is developed from the observation of empirical reality; thus general inferences are induced from particular instances” (Collins & Hussey, 2013). Induction moves from fragmentary details to construct a connected view of a situation. The starting point of inductive ("bottom-up") research is data collection and observation aimed at discerning patterns, or at the formulation of new theories (Burrell & Morgan, 1979; Leedy & Ormrod, 2014). The aim is to study new phenomena or to explore known, previously researched phenomena from a different perspective. Deduction relates more to positivism and induction to interpretivism (Saunders et al. 2009). While having different scope (Figure 8), inductive and deductive inference are not mutually exclusive, and can be combined e.g. for the development and evaluation of new theory (Gray 2008). Abductive reasoning is a composite approach that combines both deductive and inductive methods during certain stages of the research work (Cavaye, 1996; Dubois & Gadde, 2002).
The present research work primarily builds on abductive reasoning, employing both inductive and deductive methods, as described by Plano Clark and Creswell (2008). Through the inductive approach, plans are made for data collection, after which data is analysed and interpreted in search of concepts and relationships between concepts, to allow for the development of understanding and the formation of theories. Subsequently, deductive reasoning is employed to develop an experimental design, to validate the theory. The approach is similar to the example provided by Gray (2008) (Figure 9).

![Combination of deductive and inductive approaches to research](source: Gray (2008))

This choice was made, given the nature and complexity of the research question and the objectives set for the present study, and for the purposes of increasing the credibility of the findings. The combined use of the two forms of inference adds more depth to the analysis, while it allows offsetting inherent limitations of the research methods employed for the implementation of research.

### 4.2 Methods of research: Qualitative research

Another critical decision during research planning concerns the characterisation of research with regards to the type of methods applied for data collection and analysis. In view of the analysis above, the present research employs qualitative research methods. Qualitative research is aligned with the scope and objectives of the inquiry and meets the conditions discussed in previous sections. On the whole, research studies can be characterised as quantitative, qualitative or mixed (Guba & Lincoln, 1994; Denzin & Lincoln, 1994; Creswell, 2007, 2009, 2014; Willis et al., 2007; Teddlie, & Tashakkori, 2009; Hall, 2013; Mertens, 2014).
Historically, a dichotomy between qualitative and quantitative research methods is drawn, stating that qualitative and quantitative approaches serve different purposes, according to their individual merits and disadvantages. Guba and Lincoln (1994) claim that both methods may be used appropriately “with any research paradigm”. In recent decades, mixed methods research has been established as a third methodological direction, complementing the existing traditions of quantitative and qualitative research (Tashakkori & Teddlie, 1998, 2010; Teddlie & Tashakkori, 2009). Mixed methods researchers argue that the two methods are not mutually exclusive or in opposition, but can be combined in a single study design (Teddlie, & Tashakkori, 2009; Hall, 2013). Valsiner (2000) even claims that qualitative and quantitative methods are “related”. Quantitative research is typically associated with positivist or objectivist worldviews and deductive inference (Guba & Lincoln, 1994; Bryman & Bell, 2015). It employs structured methods for the collection of quantifiable data in numeric form and uses mathematical models and statistical techniques for data analysis (Denzin & Lincoln, 1994; Creswell, 2007; Willis et al., 2007). According to Novikov and Novikov (2013), quantitative methods focus on the characteristics of the phenomenon, investigating the intensity of its inherent properties, as expressed in quantitative terms. Their principal objective is to examine relationships between these variables, to produce results that are predictive, explanatory, or confirmatory.

Qualitative research is of an interpretive or critical nature and is typically associated with inductive reasoning (Creswell, 2002; Myers, 2013). Qualitative research is usually indicated when seeking to understand a situation or to develop a theory, when the focus of the research is on the description and interpretation of relationships, the generation of classifications or typologies and the generation of hypotheses (Kluge, 2000; Cohen, et al., 2002). Qualitative methods investigate phenomena through the collection, analysis, and interpretation of qualitative data: narrative or descriptive accounts, collected mostly in textual form that are not easily reduced to numbers. Typical qualitative data sources include observation and participant observation (fieldwork), interviews and questionnaires, documents and texts, and the researcher’s impressions and reactions (Myers 2013). Qualitative research implies an “interpretive, naturalistic approach to the world” (Creswell, 2007), which is aimed at assigning “significance or coherent meaning” (Neuman, 2014) to the collected data, in order to achieve situated or contextual understanding (also called hermeneutic understanding, ideographic understanding, or verstehen) rather than discover a single “truth” (Willis et al., 2007). To
interpret means to assign significance or coherent meaning (Neuman, 2014). Qualitative studies give data meaning, translate them, or make them understandable (Denzin & Lincoln, 1994; Novikov & Novikov, 2013; Neuman, 2014). Qualitative methods are inclusive, and attend to the phenomenon as a whole, being directed towards an “exploration of the totality of attributes, properties and specific features of a studied phenomenon” (Novikov & Novikov, 2013); they are flexible and contextual, assume multiple perspectives, and investigate things in their natural settings, in order to make sense of phenomena in terms of the meanings people bring to them (Willis et al., 2007). Qualitative research is recursive and fuzzy, as its methods, from technique to purpose, can evolve across the research process (Willis et al., 2007). The scientific rigour of qualitative studies is a measure of their trustworthiness, according to the criteria of credibility, transferability, dependability and confirmability (Guba, 1981; Shenton, 2004) or trustworthiness, authenticity, typicality and transferability (Holloway, & Galvin, 2016). Because of the subjective nature of qualitative data and its origin in single contexts, achieving adequate validity or reliability is often a challenge. The major criticism of qualitative research is that it is difficult to replicate and to generalise with confidence to a wider context (Myers 2013). Furthermore, researcher represents the primary tool for data collection and analysis, and can have a profound effect on the study (Willis et al., 2007).

In literature, various strategies for qualitative research exist (Saunders et al., 2009) each specific to the context and nature of research that one intends to conduct, with the help of appropriate tools and techniques for data collection and analysis. In the following sections the specific methods and strategies employed by the present research are discussed.

### 4.3 Research strategies

The choice of tools and procedures for evidence collection and analysis is an integral part of research design. In the present research the research strategy adopted, in order to answer the research questions and ultimately provide a solution to the research problem, features a combination of empirical and non-empirical procedures and activities. The non-empirical tasks set the foundations for the empirical research activities. Qualitative research strategies include case studies, ethnography, action research, content analysis, phenomenological studies. Two broad types of research design are applied with respect to evidence collection, namely, designs
that generate primary data (case study) and designs that exploit existing data (thematic analysis of secondary sources).

4.3.1 Case study research

Yin (1994) defines case study as “an empirical inquiry that investigates a contemporary phenomenon within its real-life context, especially when the boundaries between phenomenon and context are not clearly evident”. Bromley (1990) described it as a “systematic inquiry into an event or a set of related events which aims to describe and explain the phenomenon of interest”. On the whole, a case study represents a multi-perspectival investigation into a specific, and spatially delimited instance of the phenomenon, a bounded system (“case”) that is taken as a whole, in action, as it evolves, and in its real-life context, and is observed at a single point in time or over some period of time (Tellis, 1997; Morra & Friedlander, 1999; Cohen et al., 2002; Gerring, 2007; Creswell, 2007). Yin (2003) distinguishes the following types of cases: critical, unique, revelatory, representative or typical, and longitudinal case. Case study involves detailed data collection from multiple sources of evidence and in-depth analysis (Creswell, 2007) and is characterised by high “ecological validity” (Bracht & Glass, 1968). Willis et al. (2007) claim that case study research is particularist, naturalistic, thick in descriptive data, heuristic, and often inductive. This method of study is thus especially useful for both developing and testing theoretical models (Eisenhardt, 1989; Cavaye, 1996; Flyvbjerg, 2006), which are constructed and applied in real world situations respectively. Case studies are widely used in business research (Robson, 1993) and information systems research, and are considered well suited for understanding the interactions between information technology-related innovations and organisational contexts (Darke et al., 1998). The case research method is particularly suitable for exploratory studies, for discovering relevant constructs in areas where theory building at the formative stages, for studies where the experiences of participants and context of actions are critical, and for studies aimed at understanding complex, temporal processes (why and how of a phenomenon) rather than factors or causes (what). The case study method is well-suited for studying complex organisational processes that involve multiple participants and interacting sequences of events, such as organisational change and large-scale technology implementation projects (Bhattacherjee, 2012). Case studies emphasise detailed contextual analysis of a limited number of events or conditions and their relationships. The case study method entails comprehensive understanding and extensive description and analysis of the instance as a whole.
and in its context (Morra & Friedlander, 1999). Traditionally, the case study has been associated with qualitative methods of analysis. Case study research is existentially oriented because it includes the context of the phenomenon and deals more with direct observations of object reality as part of the object of study. It doesn’t assume that the phenomenon under study can be isolated from the context or that the facts or observations are independent of the laws and theories used to explain them (Steenhuis & deBruijn, 2006). Rather than having to select one of the two approaches of evidence generation, single case and cross-case studies can be viewed as complementary. At the very least, the process of case selection involves a consideration of the cross-case characteristics of a group of potential cases (Gerring & Seawright, 2007). The purposes of case study research may be exploratory, descriptive, interpretive or explanatory (Mariano, 1993). **Exploratory** case studies aim to find answers to the questions of ‘what’ or ‘who’. **Explanatory** case studies aim to answer ‘how’ or ‘why’ questions with little control on behalf of the researcher over occurrence of events (e.g. real-life situations). **Descriptive** case studies aim to analyse the sequence of interpersonal events after a certain amount of time has passed. Case studies belonging to this category usually describe culture or subculture, and they attempt to discover the key phenomena. Guba and Lincoln (1981) describe three study types: **factual**, **interpretative** and **evaluative**. In the context of evaluating World Bank projects, three main categories of case studies are identified explanatory, descriptive, and combined (Morra & Friedlander, 1999). Stake (1995) distinguishes between: **instrumental** case studies, used to provide insight into an issue; **intrinsic** case studies, undertaken to gain a deeper understanding of the case; and the **collective** case study that investigates number of cases in order to inquire into a particular phenomenon.

By and large, a case study may rely on single or multiple-case designs (Tellis, 1997), with the exploration of multiple cases (multisite research) strengthening the result and providing a firmer basis for generalisation (Huberman & Miles, 2002), and the exploration of a single or limited number of cases entailing the risk of “radical particularism” (Firestone and Herriott, 1984). The number and type of case studies depends upon the purpose of the inquiry (Stake, 1995). According to Yin (1994) case study design includes five components: the research question(s), its propositions, its unit(s) of analysis, a determination of how the data are linked to the propositions and criteria to interpret the findings. Theory is developed at the beginning of the research and subsequently tested through replications in the empirical case situations (deductive
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Analysis of case study data is generally extensive and often involves triangulation through the use of multiple data sources, methods, or investigators, in order to establish credibility (Creswell, 2007). The validity of the findings, especially when trying to determine cause and effect, is derived from agreement among the types of data sources, together with the systematic ruling-out of alternative explanations and the explanation of “outlier” results. Examining consistency of evidence across different types of data sources is a means of obtaining verification. The process of doing case study evaluations has become more participative or collaborative (Yin 1989, 1993, 1994, 1997).

A common criticism of case study research is that it is method with “high accuracy and low generalisability” (Woodside, 2010). Gerring (2007) argues that a study that is based on a “nonrepresentative sample” lacks “external validity”, i.e. it offers limited generalisability. He stresses that in order “to be a case of something broader than itself, the chosen case must be similar (in some respects) to a larger population. Otherwise - if it is purely idiosyncratic (unique) - it is uninformative about anything lying outside the borders of the case itself”. In this light, qualitative inquiry may focus on the in depth investigation of small samples, even single cases, selected purposefully (Patton, 2002).

The primary objective of conducting a case study in the present inquiry is evaluative (USAID, 2013) and illustrative, while insights revealed in its duration also served formative purposes in the development and refinement of the KDC Framework. The instance investigated (case study site) is the IMI-ADVANCE project as a whole, and its first proof-of-concept study (POC1) in particular. The scope of the case study is confirmatory. The ADVANCE case was selected purposefully, for being an “information-rich”case, whose in depth study will illuminate the questions under study (Patton, 2002), and a typical case (Flyvbjerg, 2006) that is representative of the population (see Table 7, Appendices 1 & 2). The goal of an evaluative case study is to obtain as full an understanding as possible (USAID, 2013), obtained through “extensive description and analysis of that instance taken as a whole and in its context” (Morra & Friedlander, 1999). A wide range of data collection methods were used to construct the ADVANCE case study, including desk reviews of project documents, secondary data and existing literature, focus group interviews, as well as direct and participant observation. The latter signifies that, to a certain extent, the investigator became an active, functioning member of the culture under study. Document review, secondary data analysis and observation allow for
rich, extensive description and analysis that yield a detailed, "thick description" of the case that conveys a sense of the experience of being at the site.

4.4 Methods for data collection and analysis

The methods for data collection and analysis are aligned with and contribute to the scope and objectives of the inquiry. They are determined by the methodology and are consistent with the philosophical and theoretical assumptions of the study. The present inquiry employs a combination of qualitative research methods for the collection and analysis of qualitative evidence, stemming from multiple sources. Critical in this process is the role of the researcher, not solely with regards to the decisions made, but also with respect to the implementation of the actions, since the investigator is the primary tool for data collection and analysis in qualitative research (Willis et al., 2007).

4.4.1 Sources of qualitative data

To allow for comprehensive depth and breadth of inquiry, the present research harnesses multiple sources of evidence (Sekaran, 2000; Saunders et al., 2009). The research is not envisaged as a conceptual study, but rather as an empirical investigation that relies on empirical data (Myers, 2013), and is informed by theory. Consequently, the study revolves around two broad research domains: pharmacovigilance and translation research. Willis et al. (2007) note that “from interpretivist and critical perspectives, multiple perspectives often lead to a better understanding of the situation”. For this reason, the present inquiry adopts an inclusive approach with regards the collection of data about the pharmacovigilance domain. Qualitative data from both empirical and non-empirical sources are collected. In the literature review (Chapter 2), a comprehensive investigation of the domain is pursued, targeting the current state-of-the-art and emerging directions, through the exploration of secondary and tertiary sources of evidence (scientific and grey literature: books, research project reports, regulations and guidelines, technical document, corporate, policy-oriented and other reports etc, and directories, guidebooks, manuals, handbooks, Wikipedia etc). During the ADVANCE case study, additional empirical insight is collected on the specific topic of vaccine benefit-risk analysis: key informants for the case study (expert feedback), project documents, field notes (primary data). Given the interpretative and “sense-making” orientation of the study, data is collected from human sources, but non-human sources are used as well. Human sources include expert participants in
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the field of vaccine benefit-risk analysis and regulation, engaged in various activities (workshops, focus groups, observation) as part of the case study. Non-human sources include scientific literature (articles, books, position papers etc.) from both domains of interest, and other related areas, as well as grey literature (non-peer reviewed internet publications, opinions, reports and commentaries). To further strengthen the inference capability of the study, data is collected from within the research domain and outside the field. Going beyond the confines of the field of study allows making comparisons, drawing analogies (analogical reasoning), identifying resemblances and suggesting explanations for phenomena (Willis et al., 2007). As part of the investigation of the current state and emerging trends in pharmacovigilance (Chapter 2: Literature Review), different perspectives are explored (technology, organisation, legal) in a generic or universal, and in a sector-specific way.

4.4.2 Methods of data collection

The main data collection techniques used in this research study were focus groups, group discussions and workshops, participant observation and document analysis, literature review and secondary source analysis. Different methods are employed for the collection of non-empirical data (secondary methods of data collection) and empirical data (primary methods of data collection). Efficient data collection in qualitative research, requires careful sampling. Sampling refers to the process of selecting a given number of units of analysis from a population. The dimensions of the sample population and the factors according to which the sample is drawn up are linked to the research questions being addressed (Patton, 2002). Random selection is aimed at ensuring representativeness. In purposive sampling the researcher selects participants according to the aims of the research. The data collection instruments selected for this inquiry are presented below:

4.4.2.1 Secondary data collection methods

Secondary data collection methods refer to the collection of non-empirical data. The main tool employed for this purpose was literature review.

(i) Literature review and desk research

The critical review of literature is an important part of a research project and can serve several purposes: locate the research project, from its context and background, actualise knowledge etc. (Saunders et al., 2009; Ridley, 2012). It concerns the pre-existing body of knowledge in a
particular field. Literature review is used as a source of up-to-date knowledge, as a reference for research conducted previously in the chosen field of inquiry, as well as a source of the body of theory which pertains to the selected subject area. Literature review critically explores the current state of knowledge in the subject area, its limitations, and how the undertaken research fits in this wider context (Saunders et al., 2009), thus establishing the importance of the study (Creswell, 2009). A literature review is described as the summarisation of previous research on a topic. In this process, the investigator “extracts and synthesises the main points, issues, findings and research methods which emerge from a critical review of the readings”, rather than develop an “annotated bibliography” on the subject (Nunan, 1992).

One important component of reviewing the literature is to identify relevant theories, i.e. theories that might be used to explore the questions in a scholarly study. In quantitative research, researchers often test theories as an explanation for answers to their questions. In qualitative research, however, the use of theory is much more varied and data have primacy. Saunders et al. (2009) note that in research projects that build on an inductive approach, the investigator explores data, in order to develop theories from them that they will subsequently relate to the literature. In this case, where research work does not start with predetermined theories or conceptual frameworks, a competent knowledge of the subject area is needed.

In the light of the above, the literature review undertaken in the present research had a twofold objective to: (a) collect, review and synthesise relevant information, in order to develop good knowledge and understanding of the research area, and provide early seeds for the construction of the Reference Framework (working hypotheses or Objectives) and (b) to discover and provide an insight into relevant research approaches and theories that may be appropriate to the present research questions and objectives (translation research, information systems development etc), in order to shape the Reference Framework. The approach employed for the identification of information about the area of pharmacovigilance and theories about research translation and other relevant fields, was a combination of electronic database search and snowballing methodologies (Wohlin, 2014). The scientific literature was searched through the electronic databases PubMed, ScienceDirect, Web of Science, and Google Scholar. Journal indexes were searched. Additional evidence was collected from relevant grey sources. Emphasis was placed on the review the most relevant and significant research and evidence on the topics addressed: (a) current research and emerging directions in pharmacovigilance and relevant fields; and (b)
scientific theories in relevant research areas. In the first case, traditional or narrative literature review is performed, but with an integrative objective (Neuman, 2014). Representative literature on the identified topics of interest is reviewed, critiqued and integrated in order to generate new perspectives on the domain of pharmacovigilance. In the second case, traditional or narrative literature review is performed, with a theoretical focus. The corpus of theory that exists in regard to the issues identified is examined, in order to integrate and summarise what is known in theory that may be appropriate to the present research. Selected theories and frameworks that focus on relevant topics are presented and their assumptions, logical consistency, and scope of explanation are discussed, and compared against the requirements of the present study.

4.4.2.2 Primary data collection methods

A primary data source is an original data source, where data is collected directly by the researcher for a specific research purpose or project (Salkind, 2010). Primary data collection methods refer to the collection of empirical data, and, in the present case, mainly revolve around the ADVANCE case study and the evaluation of the KDC Framework. The purpose is to collect comprehensive and in-depth information.

(i) Focus group discussions

A focus group is a method of qualitative research in which a group of people are asked about their perceptions, opinions, beliefs, and attitudes towards a product, a service, a concept, etc at the same place and at the same time. Questions are typically asked in an interactive group setting where participants are free to talk with other group members. As Quible (1998) underlines, focus groups provide investigators with valuable qualitative data not easily obtained through other means about what the group thinks about an issue. The organisation and analysis of focus group discussions can reveal the range of opinions and ideas, and the inconsistencies and variations that exist in a particular community in terms of beliefs and their experiences and practices. A focus group discussion typically involves 6 to 12 participants and a session usually lasts 1-2 hours. The participants’ comments are recorded, and these data are used for analysis and reporting. The focus group participants should share a common denominator: relevance or interest on the topic discussed, in-depth knowledge of the issue. Quality focus groups are, therefore, characterised by carefully and purposefully recruited participants, interacting in a comfortable environment, led by a skilful moderator, followed by systematic analysis and reporting (Krueger & Casey, 2002).
Kruger (1988) identifies three important phases in the process of implementing focus groups: conceptualisation, interview, and analysis & reporting. Semi-structured or unstructured topic guides are often used to collect qualitative data in focus group discussions. In the present inquiry focus group discussions were organised for the evaluation of the KDC Framework (Chapter 5).

(ii) **Participant observation**
Observational research collects information about actual behaviour in context: they are used to investigate and document what research participants do in situ using the senses. Observations are ideal when used to document, explore, and understand, as they occur, activities, actions, relationships, culture, or taken-for-granted ways of doing things. Typically, observations can be unobstructive and non-reactive, or obvious and reactive. In participant observation the investigator becomes involved, either overtly or covertly, over a lengthy period of time, in a setting culture, group, or organisation in order to study it (Salkind, 2010). According to Hudelson (1994) participant observation gives the researcher an intuitive understanding of what is happening in a culture, thus enhancing their interpretation capabilities with regards to the data being collected and maximising their ability to make valid statements about the culture being studied. She further notes that participant observation is useful when the situation of interest is hidden from the public. In the light of the above, the case study conducted in the present inquiry (ADVANCE case study) involved participant observation, being viewed as an important instrument for the collection of information for the provision of additional insight to complement and contextualise findings from other methods. An additional advantage of observation is that it can provide detailed information about the setting. This is of particularly interest to the present research, since European R&D projects involve informal exchanges among participants, and work is largely confidential, with access to most working documents and some reports being typically restricted.

(iii) **Document analysis**
The production of reports and working documents is a common activity in research projects. The implementation of research projects follows a structured approach that relies heavily on step-by-step documentation of decisions and actions. Besides formal reports detailing the outcomes of research, a large number of working documents is produced and exchanged internally, in order to describe and document the activities undertaken and the intermediate outputs of the research process among project participants. This is complemented by an extensive exchange of emails
that can provide further insight into the underlying thought processes, the individual concerns and considerations. The study and analysis of formal and informal documentary sources can thus provide additional insight to complement and contextualise findings from other methods.

(iv) Workshops
A Workshop is broadly described as a training class or seminar in which the participants work individually and/or in groups to solve actual work related tasks to gain hands-on experience. The present study was informed by workshops organised in the context of the ADVANCE project (i.e. the case study site).

4.4.3 Methods of data analysis
Aim of qualitative data analysis is to extract meaning from data. Several approaches are proposed for the analysis and interpretation of data arising from qualitative methods. By and large, qualitative researchers interpret their data in one of two ways: holistically or through coding. Holistic analysis attempts to draw conclusions based on narrative materials as a whole, without breaking the evidence into parts. Coding-based analysis implies searching data systematically for the identification and categorisation of specific observable actions or characteristics into themes and thematic categories. For the purposes of the present inquiry the thematic analysis method (Braun & Clarke, 2006) was used.

Thematic analysis is a systematic approach to the analysis of qualitative data that employs open coding in order to determine themes and sub-themes from within the data. It involves identification of themes or patterns of cultural meaning; coding and classification of data according to themes; and interpretation of the results (Mills et al., 2010). Braun and Clarke (2006) describe thematic analysis as a the process of coding that comprises six phases: familiarisation with data, generating initial codes, searching for themes among codes, reviewing themes, defining and naming themes, and producing the final report. Thematic analysis is not necessarily concerned with the frequency at which a theme occurs, i.e. a higher frequency does not necessarily mean that the theme is more important. Braun and Clarke (2006) distinguish between two kinds of themes: semantic and latent. The former refers the explicit or surface meanings, while the latter describes underlying ideas, assumptions, and conceptualisations. Thematic analysis can be theoretical or inductive, with coding and theme development being directed by existing concepts or ideas, or by the content of the data respectively.
In the present inquiry, the thematic analysis method was employed for the analysis of literature review data and case study data. A quantitative analysis approach studying the occurrence of terms (content analysis) was deemed inappropriate for this research, given the study’s focus on examining and interpreting trends, and signals and patterns in the field of pharmacovigilance and the small number of respondents in individual empirical data collection activities. An inductive perspective was assumed for the analysis of the literature review data, while empirical data was analysed using theoretical thematic analysis. Analysis was performed manually, without the use of statistical software.

5. Research plan

The present research work is directed at assisting operational improvement, decision making and strategic planning, rather than clinical research. This section describes actions to be taken to investigate the research problem: the specific procedures and techniques applied, their objectives and outputs. Aim of the present research work is to establish and validate a Reference Framework for drug safety investigations suitable for an evolving technological and social landscape. The principle function of the KDC Reference Framework is to align and coordinate the broad set of capabilities needed for setting up drug safety investigations and studies that meet particular outcomes. This goes beyond the establishment of technical capability and competence and involves a strong social dimension. From a conceptual point of view, the process for the development of a Reference Framework for collaborative, information-driven innovation in the field of pharmacovigilance is illustrated in the following figure (Figure 10):

![Figure 10. Conceptual framework of the research process](image)

The research strategy comprises the following phases:
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▸ Phase 1: Investigation of existing practices
The investigation of existing practices in the field of pharmacovigilance constitutes the starting point of the inquiry.

▸ Phase 2: From status quo to the future (envisioned directions)
The objective set for this phase is to develop an understanding of the way forward in pharmacovigilance and to provide a detailed look at important aspects of its implementation (legal, organisational, ergonomics).

▸ Phase 3: Synthesis of requirements for framework development
After having documented the status quo and the envisioned future directions, the results need to be synthesised into a set of design requirements. All views on the topics and the diverse data assets are taken into account and analysed systematically.

▸ Phase 4: Development of the Knowledge Discovery Cube Framework
The Knowledge Discovery Cube Framework is developed on the basis of the requirements specified. The process is informed by relevant models and theories from other relevant fields.

▸ Phase 5: Application & validation
For the purposes of validation of the operationalised Knowledge Discovery Cube Framework in the context of vaccine safety monitoring is discussed and validated

▸ Phase 6: Evaluation of research hypotheses
At the final stage the research hypotheses specified at the onset of the present research are revisited and discussed in retrospect.

Time horizon of the research
It should be noted that the aforementioned depiction of the research strategy as a linear path does not accurately reflect the actual research process. The present study is best viewed as a spiraling process. It follows an inherently nonlinear path, with successive passes through the steps and repetitions over different periods of time, during which new data is collected and new insights are generated (longitudinal study) (Saunders et al., 2009; Zikmund et al., 2013).

The research process comprises the following steps:
- Exploratory study of the current scientific literature and industry insights to understand the state of the art and emerging trends in pharmacovigilance.
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- **Requirements elicitation**: deriving requirements (working hypotheses) grounded in data collected from the study of literature.

- **Framework design**: exploring relevant frameworks and theories mapping requirements against existing models. The design approach has as input empirical data from the field of pharmacovigilance and also paradigms, theories, models and frameworks from the world of research, which serve as input to the development of a Reference Framework for collaborative, information-driven innovation in the field of pharmacovigilance.

- **Verification and validation**: The application of the developed framework in the area of vaccine safety monitoring. Together with the knowledge gained from the world of research, case study data is used to verify and validate that the research outcome meets the design requirements, correlates with existing knowledge from the world of science and contributes new knowledge to this field.

The underlying principles of the research plan can be described as follows:

- Multiple data sources: data is drawn from different sources, reflecting different perspectives and analysis dimensions in order to provide a comprehensive view of the domain;

- Multi-methodological approach: different methodologies are combined together as part of the present research;

- Ongoing investigation: knowledge sources are monitored throughout the lifecycle of the research;

- Iterative investigation: operating interchangeably at a theoretical and an empirical level.

The adopted research approach could be described as a combined empirical (inductive) and theory-informed (deductive) endeavour, which constantly iterates between theory and observation. It consists of inductive discovery (induction) building on thematic analysis and deductive proofing (deduction) that employs case study analysis. (Figure 11)
Figure 11. Conceptual model of the research approach

The foundations of the present research lay on the **pragmatic paradigm**, on **abductive inference** and **qualitative research** techniques (Creswell, 2003) that allow capturing the actual phenomena and developing the level of detail required to inform theories and methodologies. The use of inductive and deductive methods is as follows: **Induction** is employed as part of theory-building, in order to infer theoretical concepts and patterns from observed data. The process is incremental, synthesising cross-case and cross-sector evidence, to allow for a new understanding of the status and prospects of the research area. A variety of sources informed the research work as identified through extensive searches of the literature. The resulting deliberations draw on the findings and conclusions of scholarly research, guidelines, policy documents and reports, and on other resources from within and outside the field of health and life sciences, related to evidence-based pharmacovigilance. **Deductive work** revolves around theory-testing, the validation of concepts and patterns known from developed theory using new empirical data. It should be stressed that theory-testing is employed in a formative way, namely not just to test a theory, but also to refine, improve, and extend it. When researching a complex socio-technical phenomenon, such as the design and implementation of advanced knowledge value chains for pharmacovigilance, the principles of case study research (Dubois & Gadde, 2002) are applicable. The in-depth study of selected typical cases can provide a solid basis for the validation of the outputs.

**Observation and theory** are the two pillars of the present research, which operates interchangeably at two levels: a theoretical level and an empirical level. The theoretical level is concerned with developing abstract concepts about pharmacovigilance and relationships between
those concepts while the empirical level is concerned with testing the theoretical concepts and relationships to see how well they reflect our observations of reality, with the goal of ultimately building better theories. The preliminary stage of the research work is exploratory, and is aimed at scoping out the magnitude of pharmacovigilance data and methods and to provide an initial understanding about it. In general, exploratory research the preferred research approach for a problem that has not been clearly defined. Case study research would have been insufficient in the present case, given the complex and constantly evolving nature of pharmacovigilance. Instead, a broad perspective is adopted in order to delve into the research domain, and capture important nuances of the phenomenon of interest. This includes empirical data, studies, industry insight, regulatory and policy documents from the field of pharmacovigilance and beyond. An interpretive approach is adopted, in order to explain the findings and build a theory to fill in the unmet gap in the domain. Relevant work in the field of pharmacovigilance and theories from other domains are investigated, to form the basis and contribute knowledge to the Reference Framework.

Returning to the empirical level, the final stage of the research work is concerned with testing the theoretical concepts and relationships to assess how well they reflect observations of reality (case study-based evaluation), with the goal of ultimately building better theories. For the purposes of (external) validation, an explanatory case study is conducted. The developed framework is applied in the area of vaccine safety monitoring, in the context of the IMI-ADVANCE
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(“Accelerated development of vaccine benefit-risk collaboration in Europe”) project (Appendix 2). The ADVANCE project was selected purposefully as a case study site (Table 15), for being an information-rich case, whose in-depth study will illuminate the questions under investigation (Patton, 2002) that is a typical case, representative of the population (instrumental case study) (Stake, 1995), and based on practicality considerations (Crowe et al., 2011). ADVANCE is a public-private collaborative research project that is funded by the Innovative Medicines Initiative (IMI), a Joint Technology Initiative (public-private partnership) of the DG Research of the European Commission, representing the European Communities, and the European Federation of Pharmaceutical Industries and Associations (EFPIA). It features a multidisciplinary consortium that brings together key stakeholder groups in the area of vaccine safety: academia, regulatory agencies, public health organisations, vaccine manufacturers. ADVANCE focuses on the development and testing of methods and guidelines for the rapid delivery of reliable data on the benefits and risks of vaccines that are on the market, and centre this research work on Vaccine Pharmacovigilance. The project revolves around the federation of a variety of health care databases for safety signal detection, aiming to build an integrated and collaborative framework to bring together all relevant stakeholders across the European member states around the topics of vaccines safety and vaccination programs. Its aim is to review, develop and test methods, data sources and procedures which should feed into a blueprint of an efficient and sustainable pan-European framework that can rapidly deliver robust quantitative data for the assessment of the benefits and risks of vaccines that are on the market. For the purposes of validation ADVANCE is conducting proof of concept (POC) evaluation to test the overall concept design produced by the project including: processes, circumstances and workflows of a system that focuses on generating evidence on benefit/risk of vaccines. POC evaluation in the context of ADVANCE focuses on combining, analysing and reporting on the performance and knowledge generated during the performance of the POC experiments, to inform the reliability and sustainability of a post-ADVANCE platform, as defined in the project’s Vision and Mission.

While the ADVANCE project focuses on a specific subdomain of pharmacovigilance and has a limited scope in terms of evidence sources considered, its objective is aligned to the present research and its work lends itself to the scope of the operationalisation, practical investigation and validation of the KDC Reference Framework. ADVANCE represents a representative or
typical, and a broadly ‘revelatory’ case (Yin, 2003) for the study of the Hypotheses set in the present inquiry, as it is “information rich” and illuminative. ADVANCE exemplifies an everyday situation or form of organisation in vaccines and medicines safety monitoring and provides useful manifestations of the phenomenon studied. The ADVANCE case study represents both an illustrative example and a critical instance of the KDC framework. In its illustrative sense the ADVANCE case study is intended to provide realism, vividness, and in-depth information about the practical implementation of the Framework. As a critical instance, the case study serves the purposes of evaluation, i.e. functions as a critical test of the framework’s applicability, questioning the highly generalised assertions it contains and whether these are valid through examining one instance.

Table 15. Principal criteria for case selection

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Relevance to the topic of research</td>
<td>Appendix 1 (vaccine pharmacovigilance) vaccine pharmacovigilance is typically viewed and managed as a sub-area of medicines pharmacovigilance.</td>
</tr>
<tr>
<td>2 Relevance to the scope of research</td>
<td>Appendix 2 (scope of the ADVANCE project)</td>
</tr>
<tr>
<td>3 Information-rich case</td>
<td>Appendix 2</td>
</tr>
<tr>
<td>4 Typical case</td>
<td>Case is representative of the population (Table 7)</td>
</tr>
<tr>
<td>5 Scientific and technological excellence of project work</td>
<td>Appendix 2 (Quality of the ADVANCE project workplan &amp; partnership)</td>
</tr>
<tr>
<td>6 Excellence and representativeness of project partnership</td>
<td>Appendix 2 (Quality of the ADVANCE project workplan &amp; partnership): multidisciplinary consortium, involving the key stakeholder groups in the area of vaccine safety (regulatory agencies, public health organisations, vaccine manufacturers and academia).</td>
</tr>
<tr>
<td>7 Practicality (accessibility, cost, confidentiality etc.)</td>
<td>The participation of the Un. of Surrey in the ADVANCE consortium allows for in depth and long term study of the case, using various instruments (participant observation, document study, focus group discussions etc.) to illuminate the questions under investigation.</td>
</tr>
</tbody>
</table>

Typically, the analysis of such a case tends to be qualitative and participative/opinion based, rather than employing statistical methods. A comprehensive definition of the ADVANCE case study is provided in Table 16.

Table 16. ADVANCE case study definition

**Context:** vaccine pharmacovigilance

**Objective:** Operationalisation and empirical validation of the developed Reference Framework (KDC Framework) in the context of the ADVANCE project (formative and summative feedback)
Study design: Single instrumental case study

The case: Centred around the work of the ADVANCE project towards building an integrated and sustainable framework for the continuous monitoring of the benefit/risk of vaccines

Data collection: Holistic inquiry involving collection of in-depth and detailed data from multiple sources of information, including direct observation, participant observations, document analysis, surveys and focus group discussions.

Analysis: Thematic analysis of qualitative data

Criteria for the evaluation of case study results include credibility, transferability, dependability and conformability (Kultgen, 2010; Riege, 2003). Validity criteria for the evaluation of the Reference Framework will include aspects such as fit, relevance, workability, and modifiability (Glaser & Strauss 1967; Glaser 1978, 1998).

- **Fit** has to do with how closely concepts fit with the incidents they are representing.
- **Relevance**: A relevant study deals with the real concern of participants, evokes "grab" (captures the attention) and is not only of academic interest.
- **Workability**: The theory works when it explains how the problem is being solved with much variation.
- **Modifiability**: A modifiable theory can be altered when new relevant data are compared to existing data.

Table 17 summarises key considerations evoked during the different stages of the research process, the specific research objectives targeted, the related research hypotheses and the chapter, in which each element is discussed:

**Table 17. Phases of Research**

<table>
<thead>
<tr>
<th>Phase</th>
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<td><strong>Phase 1: Investigation of existing practices</strong></td>
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<td>1.2. What are the existing definitions, paradigms and trends?</td>
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<td><strong>Phase 2: From status quo to the future (envisioned directions)</strong></td>
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<td>2.3 What is the outlook for relevant environmental parameters?</td>
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<td>3.1 What are the design requirements a reference framework must satisfy so that it can be used to describe and assess research investigations in the area of drug safety monitoring and to guide and educate stakeholders towards the optimisation of these processes?</td>
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<td>3.2 What relevant theories reference models, frameworks or guidelines exist?</td>
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<td>4.3. Which assessment methodology will address the design requirements?</td>
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<td>4.4 Does the Framework adhere to the design requirements?</td>
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<td>5.1 How can the Framework be operationalised for the purposes of vaccine PV (in the context of the ADVANCE project)?</td>
<td>H₄</td>
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Chapter 3: Methodology of Research

<table>
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<tr>
<th>Phase</th>
<th>Considerations</th>
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<tr>
<td>context of vaccine safety monitoring</td>
<td>address the needs of the ADVANCE project?</td>
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<td>monitoring is presented and discussed.</td>
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<tr>
<td>Phase 6: Evaluation of research hypotheses</td>
<td>6.1 Does the research outcome support the research hypotheses?</td>
<td></td>
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<td>At the final stage the research hypotheses</td>
<td>6.2 What are the limitations?</td>
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<td>specified at the onset of the present</td>
<td>6.3 What additional steps need to be taken to make progress in this direction?</td>
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<td>research work are revisited and discussed</td>
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<td>in retrospect.</td>
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6. Ethical Considerations

The present research acknowledges the need to balance the value of advancing knowledge against the basic ethical principles that underpin all human subject research, as stipulated in the requirements of the code of ethics of the University. Several types of ethical issues had to be taken into consideration for the present research, although some of the typical ethical concerns associated with qualitative research is social sciences (Hadjistavropoulos & Smythe, 2001) do not apply in the present case. For instance participants do not run the risk of emotional or physical harm, of research interfering in their lives, or of negative psychological implications; the nature of the questions posed to participants is not personal etc.

Empirical data was collected in the context of the ADVANCE case study: (a) about the scope, objectives, progress, achievements and obstacles of the ADVANCE project (implementation of the POC study) and (b) from project participants about their work in the project and about the proposed KDC framework. Consequently, two categories of ethical issues are identified in the present study: ethical issues involving research participants and ethical issues concerning the ADVANCE project.

Ethical issues involving research participants

(a) Privacy, anonymity and confidentiality of research participants

The ethical protection of participants’ privacy (Neuman, 2014) is ensured by not disclosing their identity in the final result of the research (Thesis) and by keeping individual data contributed secret from the public. More specifically, the identity of experts taking part in dedicated
validation activities (focus groups) is kept confidential. No information is released in public that could permit linking specific participants to specific responses in any way. Project participants engaged in other data producing activities (e.g. survey, workshop) remain anonymous, with data presented only in an aggregate form.

(b) Consent of research participants
Obtaining the informed consent of the participants is an important requirement in qualitative research (Neuman, 2014). The principle of informed consent relates to the researcher’s responsibility to completely inform participants of different aspects of the research, about which data will be collected and how they are to be used. In the present case, the empirical part of the research work (case study) was embedded in, and aligned with the work of the ADVANCE project. The outcome of the instantiation of the KDC Framework was viewed and handled as an output of the project, and related research activities were viewed as regular project work, for which reports (internal work reports) were duly submitted. In this sense, research activities did not transcend the boundaries of the project work, to which all participants had already given their consent by participating, and all of the participants (including project management) were informed in advance about the scope of these activities and the instruments employed. Overall, the aim was to achieve a reasonable balance between over-informing and under-informing participants.

Ethical issues concerning the ADVANCE project
(a) Confidentiality of project work
The ethical protection of ADVANCE project work is ensured by not disclosing confidential information about the project. Despite the fact that participant observation and document analysis was employed extensively in the present research, involving access to and study of all project documents (including project internal reports and deliverables that are not disclosed to the public) and researcher field notes that detail aspects of the project work, research data that relate to confidential aspects of ADVANCE are also kept in confidence by the present inquiry. All confidential information about ADVANCE that was collected and reviewed in the course of this inquiry has been used only for the purposes of the study, and will be kept confidential.

(b) Beneficence of the ADVANCE project
Chapter 3: Methodology of Research

The principle of beneficence is typically associated with human subjects, with the discussion of research ethics being focused on possible negative effects on research participants. Nonetheless, in the present case, besides the welfare of participant, the beneficence of the ADVANCE project is also pursued: (i) doing no harm to the project work, and (ii) maximising the possible benefits. Research work is intended at advancing knowledge, while recognising a right of noninterference in the work of the project. The principle of non-interference is derived from a cultural postulate that to interfere in the interactions of others is actually to attempt to exert dominance over them (Prowse, 2011). For this reason, the discussion about the ADVANCE reference process map, which stems from the instantiation of the KDC Framework, only took place at the final stage of the POC1 study.

The present research is aligned with and complies with the principles and guidelines of the University of Surrey Ethics Code that guide research practice and define the line between ethical and unethical behaviour.

7. Problems and Limitations

Several risks are inherent to qualitative inquiry. Identifying potential risks and uncertainties in the research strategy, and recognising existing limitations in the decisions made regarding the plan, methods and instrumentation of research, the choice of data sources and informants etc., form an integral part of qualitative research work. In this sense, the research strategy is under continuous revision, in order to ensure the realisation of the research objectives.

The research strategy, as outlined in “Methodology” and as detailed in subsequent chapters, is the outcome of a series of strategic decisions made by the researcher, in order to ensure the feasibility, the practical workability and the integrity of the plan of research, for the purposes of achieving the research objectives set.
Chapter 4: The Knowledge Discovery Cube (KDC) Framework for pharmacovigilance innovation

"In the fields of observation chance favours the prepared mind."

Louis Pasteur, French chemist and microbiologist

1. Introduction

The present chapter discusses the development of the Knowledge Discovery Cube Framework. The development of the Reference Framework for collaborative information-driven medicines safety investigations is based on Goldkuhl (2004). Goldkuhl distinguishes three types of grounding to justify design knowledge: empirical observations, other knowledge of theoretical character and the design knowledge itself. With regards to empirical data, the present research builds on the concept of viewpoints (Kotonya & Sommeville, 1996, 1998) for the identification of important aspects, specific to the pharmacovigilance domain. The aim is to build an understanding of the pharmacovigilance ecosystem, its requirements and constraints and also its dynamics. Viewing pharmacovigilance as a static client-server system is not sufficient. The identification of direct stakeholder perspectives, coupled with indirect viewpoints (broader organisational, legal etc requirements and concerns that need to be taken into account) is imperative. In this framework, the previous chapters have shed light on the emerging landscape of drug safety investigations and described some of the overarching challenges that condition its structure and operations from a number of different viewpoints. The perspectives explored in Chapter 2 include: the technology viewpoint on the current state and emerging directions in pharmacovigilance; the information viewpoint on the knowledge value chain; a structural viewpoint on the pharmacovigilance ecosystem; a human viewpoint, investigating questions of ergonomics; and an ethical viewpoint, outlining ethical and legal considerations.

Building on the work of Chapter 2, Part A presents the elicitation of requirements: Section 1 brings together and consolidates the identified high level insights in the form of requirements and on this basis relevant/similar domains and theories are investigated to inform the Framework.
development process (Section 2, Theoretical investigation of Requirements). Section 3 discusses the findings. The development of the KDC Framework, its attributes and processes, are presented in Part B. Part C discusses the evaluation of the KDC Framework, as a combination of theoretical verification and external validation. In Section 2 verification is performed to establish the truth of the correspondence between the KDC Framework and its specification. The developed framework is examined against the requirements (requirements verification loops). Validation, aimed at establishing the fitness or worth of the KDC Framework for its operational mission, is performed empirically, in the context of the ADVANCE case study (Chapter 5).
Part A: Requirements elicitation

1. Synthesis of requirements

This section brings together and consolidates the identified high level insights in the form of requirements and on this basis investigates relevant/similar domains and theories to inform the Framework development process. Design knowledge is also explored, specifically targeting relevant system design paradigms. Specific research objectives for this stage include:

- **Understand** the science and design considerations of reference frameworks and define concepts, approaches and paradigms relevant to this study.
- **Define design requirements**: high level requirements and core objectives of the Reference Framework.
- Identify relevant theories (adjuvant theories)
- Refine design requirements: low-level requirements
- Identify relevant system design paradigms.

In this light, the key questions addressed in this section are as follows:

1. What are the design requirements a Reference Framework must satisfy so that it can be used to describe and assess research investigations in the area of drug safety monitoring and to guide and educate stakeholders towards the optimisation of these processes?
2. What relevant theories reference models, frameworks or guidelines exist?
3. Can pharmacovigilance design requirements be satisfied by existing frameworks?

Aim of Section 1 is to define the design requirements for the development of a reference framework for pharmacovigilance innovation (KDC Framework), bringing together and consolidating the identified challenges and considerations. The requirements elicitation and framework development process, including the relevant requirements verification loops, is illustrated in Figure 13.
Chapter 4: The Reference Framework

Figure 13. KDC Framework requirements elicitation

1.1 Requirements engineering for the new Reference Framework

The place to start developing a framework is to understand requirements and to assess the suitability of existing frameworks. Requirements are “statements of need intended to convey understanding about a desired result, independent of its actual realisation” (Kotonya & Sommervielle, 1996) or statements “about an intended product that specifies what it should do or how it should perform”, as described by Rogers, Sharp & Preece (2002). A distinction can be made between required, recommended, permissible and possible features.

In systems engineering and software engineering, requirements analysis encompasses those tasks that go into determining the needs or conditions to meet for a new or altered product or project, taking account of the possibly conflicting requirements of the various stakeholders, analysing, documenting, validating and managing software or system requirements.

Requirements engineering is the process of discovering, documenting and managing the requirements for a computer-based system (Sommerville & Sawyer, 1997). In requirements engineering, requirements elicitation is the practice of collecting the requirements of a system from users, customers and other stakeholders.

Hatley & Pirbhai (2013) note that several requirements definition methods provide a view that is limited on information processing (representing information exchanges) but fail to capture the complex underlying control structures. Their modelling technique combines data flow decomposition with model components constructed in the information- or control space, examining the system from two aspects: functional (information modelling and processing) and
behavioural (control states). Scenario-based approaches focus on the description of system goals, activities towards the achievement of goals, involved actors and other entities and their inter-relationships (i.e. structural, informational and functional associations between objects) (Sutcliffe, 1998). Several established requirements elicitation approaches for software-based systems build on a more abstract notion of viewpoints, as a means to organise and structure the requirements engineering activity. Methods include VORD (Viewpoint-Oriented Requirements Definition) (Araujo & Coutinho, 2003), CORE (Mullery, 1979), Leite’s early validation approach (Leite, 1989; Leite & Freeman, 1991), the VOSE (viewpoint-oriented systems engineering) framework (Finkelstein et al., 1992), etc. Ross & Schoman (1977) emphasise the importance of context analysis, functional specification, and design constraints for systems requirements analysis. Similarly, Dardenne et al. (1991) extend the notion of requirements analysis to include an acquisition step where a global model for the specification of the system and its environment is elaborated.

The present approach employs viewpoints in order to identify important aspects, specific to research translation in the pharmacovigilance domain (defining attributes).

Chapter 2 identified important dimensions of the emerging landscape in medicines safety investigations and analysed the overarching challenges that condition its structure and operations. The aim was to build an understanding of the ecosystem, its requirements and constraints. Viewing the ecosystem as a mere client-server architecture is not sufficient. The identification of stakeholder perspectives, including broader organisational, legal and other requirements and concerns that need to be taken into account, is imperative for the development of a comprehensive and pragmatic Reference Framework that effectively represents the interplay and interdependence of the many factors that influence the uptake of new evidence into medicines safety investigation practice.

1.2 Desired characteristics of the Reference Framework

The proposed Reference Framework for collaborative information-driven pharma safety investigation processes is aimed at providing a structured approach for managing the lifecycle of investigation implementations, addressing both the development and maintenance/optimisation of the investigation system. The discovery of new opportunities requires the constant interplay
between an unsolved problem and a new or emerging technology. Following is the mission statement for the Reference Framework under study:

**Mission of the Reference Framework is to capture and represent in portrayable dimensions the structural and temporal relations that exist among the underlying socio-technical elements of the investigation system.**

Objective of the Reference Framework is to establish a backdrop for continual analysis on the strategic and the operational level. Following is a listing of high-level requirements that need to be accommodated by a Reference Framework for collaborative, information-driven drug safety investigations. They are divided into two broad categories: scope of the investigation (strategic) and instantiation of the investigation (operational).

Table 18. High-level requirements

<table>
<thead>
<tr>
<th>Scope of the investigation</th>
<th>Instantiation of investigation</th>
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<tbody>
<tr>
<td>Digitisation and operationalisation, Improvement and optimisation, and Discovery:</td>
<td>• Operational effectiveness</td>
</tr>
<tr>
<td>• From existing scientific processes to digital procedures (from “as is” to digital)</td>
<td>• Organisational alignment and joint activity</td>
</tr>
<tr>
<td>• Exploring new paths</td>
<td>• Quality</td>
</tr>
<tr>
<td>• Continuous innovation: discovery</td>
<td>• Joint-up sources of knowledge: expanding evidence base</td>
</tr>
<tr>
<td></td>
<td>• Management of capacities and continuous Improvement</td>
</tr>
</tbody>
</table>

1.2.1 **Scope of the investigation**

(i) **From existing scientific processes to digital procedures: from “as is” to digital**

Translating existing investigation processes into information systems, computational procedures (i.e. algorithms that, together with data structures, constitute programs) and networked activities is a non-trivial task. It requires the identification of a model (abstraction) of the process.

(ii) **Exploring new paths**

Accommodate different investigations in line with the expanding scope of pharmacovigilance. The framework should facilitate the investigation of medicines safety from varying and novel perspectives. To deliver against this objective, the area of pharmacovigilance should be regarded
as an ecosystem, as a network of entities and their capabilities. A capability models what a business function does (its externally visible behaviour) and the expected level of performance (Homann, 2006). The combined and coordinated utilisation of capabilities provided by different organisations can produce new insight. While signal detection and analysis remain the focal point of medicines safety systems, there are other aspects of drug safety that have been rather neglected until now, which should be included in monitoring latent and long-term effects of medicines, for instance: detection of drug interactions; measurement of the environmental burden of medicines used in large populations; assessment of the contribution of ‘inactive’ ingredients (excipients) to the safety profile; comparison of the safety profiles of similar medicines; surveillance of the adverse effects on human health of drug residues in animals; and other. Furthermore, services to third parties beyond the typical boundaries of pharmacovigilance need be accommodated (e.g. pharmacovigilance as a service to clinical practice and therapy).

The handling of new investigations starts as an exploratory process. This may involve the formation of time-limited multidisciplinary teams specifically tailored to the requirements of the study project. Teams may use iterative trial and error to plan the investigation and produce and validate a study protocol to allow for the development of an investigation.

The Reference Framework should be comprehensive and flexible, not prescriptive of specific work methods.

(iii) Continuous innovation: discovery

Striving for the digitisation and continuous improvement of established safety investigation practices or of underserved and neglected safety questions, while critical, is not sufficient. Pharmacovigilance mechanisms need to pursue continuous innovation: discover new “knowledge paths”, new insights for new purposes. Namely, they need to employ research to discover both the question and the application, while exploring the capabilities of data evidence and technologies. Boer & Gertsen (2003) describe continuous innovation as “the on-going interaction between operations, incremental improvement, learning and radical innovation aimed at effectively combining operational effectiveness and strategic flexibility, or exploitation and exploration”. The Reference Framework should serve as basis for continual analysis and exploitation of innovation opportunities.

Summarising the three objectives stated above, digitisation & operationalisation, improvement & optimisation, and discovery form the core applications of the Reference
Framework. From a knowledge discovery perspective this implies that the Reference Framework should support both deductive (hypothesis-based) and inductive (pattern-based) reasoning to accommodate any safety investigation where we look for:

- **What we know and know how** (known causal associations and methods);
- **What we know but don’t know how** (causal associations presumed to be known, but methods are unknown);
- **What we don’t know** (unknown concepts and causal associations).

In the first two cases researchers reason from known premises, or premises presumed to be true, to a certain conclusion. The third case takes a “test and learn” approach, exploring data evidence and relevant methods to extract knowledge and insight. In this light the following taxonomy of innovation valorisation models can be defined (Table 19):

<table>
<thead>
<tr>
<th>Innovation valorisation model</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>The protocol model</td>
<td>Conventional “analog” medicines safety investigation processes are transformed into “digital” knowledge-driven value chains, by assessing and aligning the scientific protocol with data evidence and required capabilities (combinatorial use of innovation).</td>
</tr>
<tr>
<td>The problem-solving model</td>
<td>Additional medicines safety questions are addressed through the design and development of new knowledge discovery practices, grounded on new technologies and new sources of evidence (exploratory use of innovation).</td>
</tr>
<tr>
<td>The validation model</td>
<td>New medicines safety insights are generated by exploring the usefulness and application potential of emerging innovations, leading to the development of new protocols for new questions (transformational use of innovation).</td>
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### 1.2.2 Instantiation of investigation

**(i) Operational effectiveness**

An in-depth investigation of the socio-technical ramifications of knowledge discovery is imperative in order to develop effective work methods for knowledge extraction in real-life situations. Causal mechanisms exist between a planned investigation and the context in which it is implemented. Contextual factors which affect the implementation and the scientific and practical validity of outcomes. In a given context, the Reference Framework should allow safety monitoring mechanisms to devise and implement situated investigation plans (methods and
instruments translated/adapted to local context), aligning relevant, available information sources and socio-technical capacities to the needs of the investigation, in order to achieve value.

The Reference Framework should enable the effective management of investigations, and help mitigate risks associated with strategic planning and prioritisation, staffing and team formation, data collection, information integration, governance and leadership, integration of technologies, trust in data use etc. This is not to be seen as a mere e-service development task or as an operational improvement exercise (use of digital technology to provide efficiencies), but as an innovation process, translating research findings into practice.

(ii) Organisational alignment & joint activity

Among the key challenges are knowledge sharing and connectivity between people, so as to facilitate the sharing and use of unarticulated knowledge. The framework should facilitate the effective organisation and governance of the investigation. During an investigation there exists both technical and organisational interdependence between stakeholders. Teams created from many functional areas and from different organisations come together to plan investigations, solve issues and create value. Different types of collaboration around drug safety questions are possible. The pattern of collaboration is typically characterised by tight couplings in individual investigations (study “projects”) and loose couplings in permanent networks (one directional, regulation-prescribed reporting). Both the Knowledge Value Collective (KVC) and the Knowledge Value Alliance (KVA) as described in the Knowledge Value framework (Bozeman and Rogers, 2000a, 2000b; Bozeman et al., 1998; Rogers and Bozeman, 2000) need be accommodated. Established investigation practices call for the development of coordination mechanisms (permanent or investigation-specific) for handling complexities and inter-organisational adaptations. Connectivity and interoperability are key enablers in this effort, exemplified in the paradigm of the pharmacovigilance ecosystem. Key questions include:

● Given a set of research questions, are there effective strategies for accessing and aggregating knowledge sources, for linking and mobilising institutions, network actors and individuals, for putting in place computational and other infrastructure need?

● Are the human, organisational and technical resources in place to produce a valid protocol for the investigation and move the investigation from science and research to application?

● Is there a sound governance structure?
The framework should promote pharmacovigilance knowledge development, building on a Joint Innovation Strategy, with stakeholders collaboratively exploring and exploiting the affordances of modern technologies to achieve more together. This involves connectivity and discourse among people, in order to facilitate the sharing and use of unarticulated knowledge. Digital congruence within organisations is imperative (Burke et al., 2007; Barnes, 2011; Kiron et al., 2016). Culture, people, structure, and tasks should be aligned with each other, with company strategy, and the challenges of a constantly changing digital landscape.

(iii) Quality

Provide the means to ensure the quality of the investigation. It is important to be able to detect or anticipate critical issues as early as possible (moving quality assurance effort up to the early phases of development). Issues including scientific validity, quality standards, regulatory compliance and legal robustness need to be put in perspective, and allow to establish success criteria, with regular checkpoints for measuring performance against these criteria.

(iv) Joint-up sources of knowledge: Expanding evidence base

The framework should accommodate an expanding evidence base. New sources of information must be introduced, analyses of stakeholder practice presented, and artifacts produced, accompanied by theories of how they might enhance meaning-making. Data may be drawn from different sources and bound by specific constraints that relate to their type, provenance, quality, etc. Besides spontaneous reporting systems and other methods of passive pharmacovigilance, data collection for active pharmacovigilance could span the physical (through the use of machine sensors), social (through social network technologies) and cyber (e.g. through the use of Web search technologies) environment. The Reference Framework should address the challenges of information integration, promote an understanding of the strengths and limitations of data sources and enable their proper use.

(v) Management of capabilities & continuous Improvement

The framework should allow stakeholders to effectively manage their capabilities, in view of emerging needs or in response to changes in core components of an investigation.

According to USAID (Tool, 2009), and in line with the four-tier hierarchy of needs proposed by Potter and Brough, the capacities and resources that are required for developing and sustaining a functional pharmacovigilance and medicine safety system span four levels: structures,
systems, and roles; staff and infrastructure; skills; and tools. In the field of business, innovation may be in response to or anticipating demand (“market readers” and “need seekers”), or to technology drivers (i.e. technology that create an improvement over one or more existing technologies). Narasihmhalu (2012) defines Innovation Triggers as market shifts and/or technology shifts that create opportunities for successful business innovations. Examples of market shift include the emergence of new user groups, regulations or deregulations etc. Sustained innovation requires purposely defined processes to guide or build innovation capabilities in organisations. According to Essmann & Du Preez (2009) innovation capability areas include: innovation process (referring to lifecycle execution), knowledge and competency, (referring to knowledge exploitation) and organisational support (referring to organisational efficacy). The aim is to: (a) ensure that the complete innovation lifecycle of an initiative is efficiently and effectively managed and executed to continuously and concurrently realise successful innovative outputs; (b) ensure the creation, consolidation, diffusion and utilisation of relevant knowledge to support the activities of innovation initiatives; and (c) ensure an innovation-conducive organisational environment with consideration for strategy, climate, culture, leadership, structure, etc. Organisations need to incorporate elements of foresight to provide a deeper, wider view of the operating environment, alerts to potential new opportunities and warning of emerging threats. Gartner’s Innovation Management Maturity Model for enterprises (Fenn & Harris, 2011) comprises five levels of maturity (reactive, active, defined, performing and pervasive) and follows traditional capability maturity model concepts in its approach. Table 20 summarises the principal (core) objectives that need be accommodated by the Reference Framework.

Table 20. Principal objectives of the KDC Framework

<table>
<thead>
<tr>
<th>Objective</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>The implementation of the knowledge discovery process spans across the technical and the social continuum. The system needs to leverage technology and state-of-the-art tools to advance the investigation, also balancing social and organisational aspects.</td>
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<tr>
<td>2</td>
<td>The knowledge discovery process combines tacit and explicit knowledge: data evidence and scientific judgment to produce insight (e.g. to infer causation). This creates the need for the availability of places of interaction, equipped with the appropriate tools for “knowledgeable stakeholders” to convene and deliberate.</td>
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Chapter 4: The Reference Framework

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<tr>
<th>Objective</th>
<th>Description</th>
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<tr>
<td>3</td>
<td>For the participating stakeholders, the knowledge discovery process is a continuous learning process. As technologies evolve and environmental circumstances change so must investigations learn from experience and adapt to the new circumstances: exploit the opportunities created in order to improve performance and mitigate potential risks.</td>
</tr>
<tr>
<td>4</td>
<td>Technology creates new capabilities for medicines safety research moving towards data-intensive processes. The feasibility of such investigations in the digital pharmacovigilance ecosystem needs to be assessed and verified at the onset of a new investigation.</td>
</tr>
<tr>
<td>5</td>
<td>During an investigation, resources internal and external to the participating organisations are mobilised, creating technical and organisational interdependence among stakeholders.</td>
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<tr>
<td>6</td>
<td>Stakeholders should be able to handle innovations and changes in core components of an investigation in an effective and timely manner.</td>
</tr>
<tr>
<td>7</td>
<td>Stakeholders should be able to recognise emerging innovations and changes that could affect investigations.</td>
</tr>
<tr>
<td>8</td>
<td>Stakeholders should seek new knowledge, explore new directions to improve the quality and expand the scope of medicines safety</td>
</tr>
<tr>
<td>9</td>
<td>Stakeholders should be able to assess the success of implemented investigations.</td>
</tr>
</tbody>
</table>

2. Theoretical investigation of Requirements

2.1 Principal Objectives mapped on Theories

Goldkuhl (2004) specifies a need for multiple grounding of design theories in external theories, reference theories, value theories, etc. In order to accommodate the identified requirements, and meet objectives, the Reference Framework needs to draw from several domains and theories. Aim of the present section is to illustrate the multiple theoretical perspectives that relate to the research problem. In principle, theories explicate the characteristics of an artefact and its interaction with the environment that result in the observed performance (March & Smith, 1995). The identified adjuvant theories provide valid insight for addressing and refining the core objectives of the Reference Framework:

**Objective 1:** The implementation of the knowledge discovery process spans across the technical and the social continuum. The system needs to leverage technology and state-of-the-art tools to advance the investigation, also balancing social and organisational aspects.

**Socio-technical theory (AdjT.1.1)**

The socio-technical systems (STS) theory (Trist and Bamforth, 1951; Mumford 1995), recognising the existence of a two-way relationship between people and machines, argues that
the effective design of technology-based work processes can only be achieved through the simultaneous optimisation of both technical and social elements. The technical subsystem comprises the devices, tools and techniques employed. The social system comprises the employees (at all levels) and the knowledge, skills, attitudes, values and needs they bring to the work environment as well as the reward system and authority structures that exist in the organisation. The design process should aim at the joint optimisation of the technical and the social subsystem. In this context, the diamond model created by Professor Harold J. Leavitt (1965) focuses on organisational behaviour, the dynamics of organisational change and the interaction of four interdependent components found in any business: the people, the goals/tasks, the structure and the technology. Leavitt’s theory states that a change made in any one area will impact the entire system. An overall strategy is thus required to accommodate change and mitigate risks.

**Systems theory (AdjT.1.2)**

Systems theory adopts a vision of organisations as systems with the aim of analysing the relationship between organisations and their environment (Mele et al., 2010). Systems theory provides a general analytical perspective for conceptualising and studying organisations holistically, as “a complex of interacting elements” (von Bertalaffy, 1968), i.e. a set of interrelated elements that turn inputs into outputs through processing. A system can be either closed or open, but most approaches view an organisation as an open system that interacts with its environment, and one that can acquire qualitatively new properties through emergence, resulting in continual evolution. An open system interacts with its environment by way of inputs, throughputs, and outputs.

**Work System theory (AdjT.1.3)**

Work system theory (Alter, 2006; 2013) is the set of ideas that forms the basis of the work system method (WSM) for analysing and designing systems in organisations. A **work system** is a system in which human participants and/or machines perform work using information, technology, and other resources to produce products and services for internal or external customers. A static view of a work system is represented by the work system framework. A dynamic view of how a work system changes over time is represented by the **work system life cycle model** (WSLC). The WSLC is an iterative model based on the assumption that a work system evolves through a combination of planned and unplanned changes. The planned changes
occur through formal projects with initiation, development, and implementation phases. Unplanned changes are ongoing adaptations and experimentation that change aspects of the work system without performing formal projects.

**Theory of Deferred Action (AdjT.1.4)**

The theory of deferred action is a design and action theory that informs design practice. It is aimed at facilitating the design of IT artefacts that will be used by individuals and organisations to act purposefully or to achieve objectives. The theory of deferred action provides understanding of systemic emergence to design complex adaptive systems (Patel, 2006). It recognises that IT artefacts are used in social systems that are emergent. Since social systems are emergent, rationally designed IT artefacts need to grow along with emerging social systems. This growth is enabled by deferred design, the mechanism built into the IT artefact that permits actors, called active designers, to **design the IT artefact in situ on an ongoing basis**. The effect of emergence on rational design is called deferred action. **Deferred action is the ability of actors to shape the IT artefact in live context.**

**Social shaping of technology (AdjT.1.5)**

The Social Shaping of Technology theory (Williams & Edge, 1996) examines the relationship between technology and society and lists political, social organisational and cultural factors among the determinants of innovation. The **Social Construction of Technology** theory proposed by Pinch and Bijker (1984) argues that technological artefacts are socially constructed by social groups and that ‘success’ and ‘failure’ are interpreted and evaluated differently by ‘relevant social groups’ with differing and sometimes entirely conflicting objectives, goals and intentions. Social constructivists argue that technology does not determine human action, but that rather, human action shapes technology. The **Actor-Network Theory** (Law, 1992; Latour, 1996) investigates how material–semiotic networks come together to act as a whole. It identifies central actors who form elements of heterogeneous networks (meaning networks that contain many dissimilar elements) of interest. These coextensive networks comprise both social and technical parts, which are treated as inseparable. Actor-network theory claims that any actor, whether person, object (including computer software, hardware, and technical standards), or organisation, is equally important to a social network. As such, societal order is an effect caused by an actor network running smoothly and begins to break down when certain actors are removed.
Stakeholder theory (AdjT.1.6)
The Stakeholder theory to strategic management (Freeman, 1984) investigates the interests of the various stakeholders in an organisation. It argues that every legitimate person or group participating in the activities of a firm do so to obtain benefits and that the priority of the interests of all legitimate stakeholders is not self-evident. The Technological Frames of Reference theory investigates interpretive processes related to IT in organisations, acknowledging that users are part of the technology. Orlikowski and Gash (1994) defined technological frames as the knowledge and expectations that guide actors’ interpretations and actions related to technological artefacts. They argued that social groups have shared frames and that differences in these groups’ frames can inhibit effective deployment of a technology.

Technology-organisation-environment framework (AdjT.1.7)
Technology-organisation-environment theory describes that the process by which a firm adopts and implements technological innovations is influenced by the technological context, the organisational context, and the environmental context (Tornatzky and Fleisher 1990). The technological context includes the internal and external technologies that are relevant to the firm (equipment and processes). The organisational context refers to the characteristics and resources of the firm, including the firm’s size, degree of centralisation, degree of formalisation, managerial structure, human resources, amount of slack resources, and linkages among employees. The environmental context includes the size and structure of the industry, the firm’s competitors, the macroeconomic context, and the regulatory environment.

Fit-Viability theory (AdjT.1.8)
The Fit-Viability theory (Tjan, 2001) was originally proposed for evaluating organisational adoption of Internet initiatives on two dimensions: (1) Fit measures the extent to which new network applications are consistent with the core competence, structure, value and culture of organisation and (2) Viability measures the extent to the value-added potential of new network applications, requirements of human resource, capital needs etc.

Task-technology fit theory (AdjT.1.9)
Task-technology fit theory (Goodhue & Thompson, 1995) states that IT is more likely to have a positive impact on individual performance and be used if the capabilities of the IT match the tasks that the user must perform. Factors determining task-technology fit include: quality,
locatability, authorisation, compatibility, ease of use/training, production timeliness, systems reliability, and relationship with users.

**Organisational culture (AdjT.1.10)**

The Business Dictionary (2016) defines organisational culture as encompassing values and behaviours that "contribute to the unique social and psychological environment of an organisation. One of the most popular organisational culture frameworks is that of Edgar Schein (1988), who described culture on three levels: (1) **Artifacts** – Artifacts are difficult to measure and they deal with organisational attributes that can be observed, felt and heard as an individual enters a new culture. (2) **Values** – This level deals with the espoused goals, ideals, norms, standards, and moral principles and is usually the level that is usually measured through survey questionnaires. (3) **Underlying assumptions** – This level deals with phenomena that remain unexplained when insiders are asked about the values of the organisational culture. Information is gathered in this level by observing behaviour carefully to gather underlying assumptions because they are sometimes taken for granted and not recognised. According to Schein (1988), the essence of organisational culture lies in this level.

**Contingency theory (AdjT.1.11)**

In a general sense, contingency theories are a class of behavioural theory that contend that there is no one best way to structure and manage organisations and that an organisational/leadership style that is effective in some situations may not be successful in others (Fiedler, 1964). In other words: Structure and management are contingent on the nature of the environment in which the organisation is situated. The **design of an organisation and its subsystems must 'fit' with the environment.** The needs of an organisation are better satisfied when it is properly designed and the management style is appropriate both to the tasks undertaken and the nature of the work group. Contingency Theory argues for finding the best organisation structure under a given set of environmental circumstances (Weill & Olson, 1989).

**Objective 2:** The knowledge discovery process combines tacit and explicit knowledge: data evidence and scientific judgment to produce insight (e.g. to infer causation). This creates the need for the availability of places of interaction, equipped with the appropriate tools for “knowledgeable stakeholders” to convene and deliberate.

**Organisational knowledge creation theory (AdjT.2.1)**
Nonaka’s (1994) dynamic theory of organisational knowledge creation states that organisational knowledge is created through a continuous dialogue between tacit and explicit knowledge that includes four types interaction: socialisation, combination, internalisation and externalisation. Explicit knowledge is codified knowledge transmittable in formal, systematic language whereas tacit knowledge is personalised knowledge that is hard to formalise and communicate and deeply rooted in action, commitment and involvement in context (Polanyi, 1962).

**Knowledge-based theory of the firm (AdjT.2.2)**

The knowledge-based theory of the firm considers knowledge as the most strategically significant resource of the firm (Grant, 1996). This knowledge is embedded and carried through multiple entities including organisational culture and identity, policies, routines, documents, systems, and employees. Because knowledge-based resources are usually difficult to imitate and socially complex, heterogeneous knowledge bases and capabilities among firms are the major determinants of sustained competitive advantage and superior corporate performance.

**Objective 3:** For the participating stakeholders, the knowledge discovery process is a continuous learning process. As technologies evolve and environmental circumstances change so must investigations learn from experience and adapt to the new circumstances: exploit the opportunities created in order to improve performance and mitigate potential risks.

**Organisational learning theory (AdjT.3.1)**

Organisational learning theory states that, in order to be competitive in a changing environment, organisations must change their goals and actions in response to a change in circumstances to reach their objectives. The theory builds on the notions of Organisational Effectiveness and Performance Gap, which describe the degree to which expected outcomes, given environmental conditions, match actual outcomes, and the degree to which they do not match, respectively. (Argyris, 1977; Levitt & March, 1988; Huber, 1991).

**Complexity theory in organisations (AdjT.3.2)**

Also called complexity strategy or complex adaptive organisations, this theory refers to the use of the study of complexity systems in the field of strategic management and organisational studies (Styhre, 2002; Grobman, 2005). Complexity theory emphasises interactions and the accompanying feedback loops that constantly change systems. While claiming that systems are unpredictable, with many independent agents interacting with each other in multiple ways, the
theory states that systems are also constrained by order-generating rules, namely, that there is a hidden order to their behaviour and evolution (self-organising, complex systems). Complex adaptive system models, aimed at systemising complexity, identify four key elements: agents with schemata, self-organising networks sustained by importing energy, coevolution to the edge of chaos, and system evolution based on recombination (Anderson, 1999). Anderson (1999) concludes that “strategic direction of complex organisations consists of establishing and modifying environments within which effective, improvised, self-organised solutions can evolve”.

Objective 4: Technology creates new capabilities for medicines safety research moving towards data-intensive processes. The feasibility of such investigations in the digital pharmacovigilance ecosystem needs to be assessed and verified at the onset of a new investigation.

Computability theory (AdjT.4.1)
Computability theory deals with whether a problem can be solved, regardless of the resources required (Cooper, 2003). Computability is the ability to solve a problem in an effective manner (determine the problem’s decidability and effective calculability). This is closely linked to the existence of an algorithm to solve the problem.

Process virtualisation theory (AdjT.4.2)
Despite the steady migration of physical processes to virtual environments, some processes have proven to be more suitable for virtualisation than others. Process virtualisation theory (Overby 2008) proposes a set of constructs and relationships to explain and predict how suitable a process is to being conducted in a virtual environment.

Computational complexity theory (AdjT.4.3)
This theory examines the computational difficulty of computable functions, i.e. the resources required during computation to solve a given problem (Hartmanis & Stearns, 1965). The most common resources are time (duration) and space (processing memory).

Systemic capacity building (AdjT.4.4)
According to Potter and Brough (2004), capacity building is achieved by applying a four-tier hierarchy of needs: (1) structures, systems and roles, (2) staff and facilities, (3) skills, and (4) tools. Emphasising systemic capacity building would improve diagnosis of sectoral shortcomings
in specific locations, improve project/programme design and monitoring, and lead to more effective use of resources.

**Objective 5:** During an investigation, resources internal and external to the participating organisations are mobilised, creating **technical** and **organisational interdependence** among stakeholders.

**Resource dependency theory (AdjT.5.1)**

The resource dependency theory (Pfeffer & Salancik, 1978) highlights the importance of external resources for organisations and how this affects **their structure and patterns of behaviour to acquire and maintain needed external resources** (forming collaborations, alliances, joint ventures, etc, or striving to overcome dependencies). The acquisition of the external resources needed by an organisation signifies a change in the organisation’s power over equilibrium against other organisations (decreasing the organisation’s dependence on others and/or by increasing other’s dependency on it).

**Objective 6:** Stakeholders should be able to handle innovations and **changes** in core components of an investigation in an effective and timely manner.

**Theory of disruptive innovation (AdjT.6.1)**

The Theory of disruptive innovation (Christensen, 1997) used the term to describe innovations that create new markets by discovering new categories of customers. Originally, the term disruptive technology was used (Bower & Christensen, 1996), which Christensen later replaced with disruptive innovation, recognising that few technologies are intrinsically disruptive or sustaining in character and that the disruptive impact is caused by the business model that the technology enables. Christensen contrasted disruptive innovation with sustaining innovation, which simply improves existing products.

**Absorptive capacity theory (AdjT.6.2)**

Absorptive capacity is an organisation’s ability to identify, assimilate, transform, and apply valuable external knowledge. Cohen & Levinthal (1989; 1990) described it as an organisation’s "ability to recognise the value of new information, assimilate it, and apply it to commercial ends". Absorptive capacity is a limit to the rate or quantity of scientific or technological information that an organisation can absorb.
Organisational information processing theory (AdjT.6.3)
Galbraith’s (1973; 1974) information processing theory on the design of organisational structures proposes that each organisation must build an organisational structure that can handle and process the different uncertainties that the organisation is facing. The theory examines the fit between an organisation’s information processing needs and information processing capability, as a determinant of performance and discusses strategies to cope with uncertainty and increased information needs.

Dynamic capabilities (AdjT.6.4)
In organisational theory, dynamic capability is the capability of an organisation to purposefully adapt their resource base. Teece et al. (1997) define dynamic capabilities as ‘the ability to integrate, build, and reconfigure internal and external competencies to address rapidly-changing environments’.

Instrumentalisation theory (AdjT.6.5)
Feenberg (1991) claims that that the technical and the social cannot be separated without losing sight of important dimensions. Feenberg’s instrumentalisation theory in design holds that technology must be analysed at two levels, the level of the original functional relation to reality and the level of design and implementation. At the first level, we seek and find affordances that can be mobilised in devices and systems by decontextualising the objects of experience and reducing them to their useful properties. At the second level, designs are introduced that can be integrated with other already existing devices and systems and with various social constraints such as ethical and aesthetic principles. The primary level simplifies objects for incorporation into a device while the secondary level integrates the simplified objects to a natural and social environment.

Objective 7: Stakeholders should be able to recognise emerging innovations and changes that could affect investigations.

Futures Studies & Foresight (AdjT.7.1)
Futures studies is the study of postulating possible, probable, and preferable futures and the worldviews and myths that underlie them. It includes analysing the sources, patterns, and causes of change and stability in an attempt to develop foresight and to map possible futures. Foresight encompasses a range of approaches: (1) forecasting, forward thinking and prospectives (identify
futures), (2) strategic analysis and priority setting (planning), and (3) dialogue and orientations (networking and agreement). When applied by organisations, corporate foresight is used to support strategic management, identify new business fields and increase the innovation capacity of a firm (Daheim & Uerz, 2006; Rohrbeck et al., 2009; Rohrbeck & Gemünden, 2011).

Objective 8: Stakeholders should seek new knowledge, explore new directions to improve the quality and expand the scope of medicines safety

Concept-knowledge theory (AdjT.8.1)
The concept-knowledge theory or C-K theory of innovative design reasoning (Hatchuel & Weil, 2002; 2003; 2009) is both a design theory and a theory of reasoning in design. It defines design reasoning as a logic of “expansion processes”, i.e. a logic that organises the generation of unknown objects. Making a distinction between the space of concepts (C) and the space of knowledge (K). A concept is defined as a proposition without a logical status in the K-Space, which includes all propositions with a logical status, according to the available knowledge. The theory defines the process of design as a double expansion of the C and K spaces through the application of four types of operators: C→C, C→K, K→C, K→K. C-expansions represent "new ideas", and K-expansions which are necessary to validate these ideas or to expand them towards successful designs. Acting on the C-K theory, collaborative creativity methods build on four main dimensions: (i) explore the whole conceptual potential of the initial concept, (ii) involve and support people in a rule-breaking process, (iii) enable relevant knowledge activation, acquisition and production, and (iv) manage collective acceptance and legitimacy of rules (re)building.

Objective 9: Stakeholders should be able to assess the success of implemented investigations.

Information Systems success model (AdjT.9.1)
This information systems (IS) theory seeks to provide a comprehensive understanding of IS success by identifying, describing, and explaining the relationships among six of the most critical dimensions of success along which information systems are commonly evaluated: information quality, system quality, service quality, system use/usage intentions, user satisfaction, and net system benefits (DeLone & McLean 1992). The theory stipulates that a system can be evaluated in terms of information, system, and service quality. These characteristics affect the subsequent
use or intention to use and user satisfaction. As a result of using the system, certain benefits will be achieved. The net benefits will (positively or negatively) influence user satisfaction and the further use of the information system.

Table 21 summarises the insights drawn from the theoretical investigation of requirements, namely, the needs to be accommodated by the KDC Framework, according to the analysis of the identified adjuvant theories.

Table 21. Refined requirements

<table>
<thead>
<tr>
<th>No</th>
<th>Refined (Low level) requirements</th>
<th>Theoretical insight</th>
<th>Adjuvant Theory</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>enable the simultaneous optimisation of both technical and social elements in the design of pharmacovigilance innovations</td>
<td>effective design of technology-based work processes requires the <strong>simultaneous optimisation</strong> of both technical and social elements</td>
<td>AdjT.1.1</td>
</tr>
<tr>
<td>2</td>
<td>enable the balancing of interdependent components (people, goals/tasks, structure and technology)</td>
<td>organisational behaviour and the dynamics of organisational change are conditioned by the interaction of <strong>four interdependent components</strong>: people, goals/tasks, structure and technology. Change made in any one area will impact the entire system.</td>
<td>AdjT.1.1</td>
</tr>
<tr>
<td>3</td>
<td>analysis of pharmacovigilance innovation as an open system</td>
<td>organisation is an open system interacting with its environment, and that they can acquire qualitatively new properties through emergence, resulting in continual evolution</td>
<td>AdjT.1.2</td>
</tr>
<tr>
<td>4</td>
<td>enable the analysis of planned and unplanned changes in the involved work systems, associated with pharmacovigilance innovation</td>
<td>work system evolves through a combination of planned and unplanned changes. The planned changes occur through formal projects with initiation, development, and implementation phases. Unplanned changes are ongoing adaptations and experimentation that change aspects of the work system</td>
<td>AdjT.1.3</td>
</tr>
<tr>
<td>5</td>
<td>allow for continuous and in situ analysis of the PV innovation instantiation</td>
<td>designed IT artefacts need to grow along with emerging social systems, in situ and on ongoing basis</td>
<td>AdjT.1.4</td>
</tr>
<tr>
<td>6</td>
<td>ensure relevance of outcomes to stakeholder groups</td>
<td>Human action shapes technology. Technological artefacts are socially constructed by social groups and ‘success’ and ‘failure’ are interpreted and evaluated differently by ‘relevant social groups’</td>
<td>AdjT.1.5</td>
</tr>
<tr>
<td>7</td>
<td>enable the joint analysis of social and technical parts</td>
<td>material–semiotic networks come together to act as a whole. These coextensive networks comprise both social and technical parts, which are treated as inseparable. Any actor, whether person, object (including computer software, hardware, and technical standards), or organisation, is equally important to a social network.</td>
<td>AdjT.1.5</td>
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### Chapter 4: The Reference Framework

<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>allow for the identification and accommodation of the needs of individual stakeholders and groups</td>
<td>Interests of the various stakeholders in an organisation. It argues that every legitimate person or group participating in the activities of a firm do so to obtain benefits</td>
<td>AdjT.1.6</td>
</tr>
<tr>
<td>9</td>
<td>allow for synthesis and consolidation of individual group perspectives</td>
<td>Social groups have shared frames (knowledge and expectations) and differences in these groups’ frames can inhibit effective deployment of a technology.</td>
<td>AdjT.1.6</td>
</tr>
<tr>
<td>10</td>
<td>enable the analysis of the innovation’s relevance to the technological, organisational and environmental context</td>
<td>The process by which a firm adopts and implements technological innovations is influenced by the technological context, the organisational context, and the environmental context</td>
<td>AdjT.1.7</td>
</tr>
<tr>
<td>11</td>
<td>enable the analysis of the innovation’s fitment and viability</td>
<td>Evaluating organisational adoption of Internet initiatives on two dimensions: Fit (consistent with the core competence, structure, value and culture of organisation) and Viability (value-added potential)</td>
<td>AdjT.1.8</td>
</tr>
<tr>
<td>12</td>
<td>enable the analysis of the effects of innovation on both a macro- and a micro-level.</td>
<td>IT is more likely to have a positive impact on individual performance and be used if the capabilities of the IT match the tasks that the user must perform.</td>
<td>AdjT.1.9</td>
</tr>
<tr>
<td>13</td>
<td>enable the analysis of the effects of organisational culture</td>
<td>Organisational culture (artifacts, values, underlying assumptions) encompasses values and behaviours that &quot;contribute to the unique social and psychological environment of an organisation.&quot;</td>
<td>AdjT.1.10</td>
</tr>
<tr>
<td>14</td>
<td>ensure relevance of governance and organisation structures to the implementation environment</td>
<td>Design of an organisation and its subsystems (Structure and management) must 'fit' with the environment.</td>
<td>AdjT.1.11</td>
</tr>
<tr>
<td>15</td>
<td>allow for continuous discourse and exchange among stakeholders</td>
<td>Organisational knowledge is created through a continuous dialogue between tacit and explicit knowledge</td>
<td>AdjT.2.1</td>
</tr>
<tr>
<td>16</td>
<td>enable the harnessing of organisational knowledge</td>
<td>Organisational knowledge is embedded and carried through multiple entities including organisational culture and identity, policies, routines, documents, systems, and employees.</td>
<td>AdjT.2.2</td>
</tr>
<tr>
<td>17</td>
<td>allow for continuous assessment of effectiveness and the identification performance gap</td>
<td>Organisations must change their goals and actions in response to a change in circumstances to reach their objectives. (Organisational Effectiveness, Performance Gap)</td>
<td>AdjT.3.1</td>
</tr>
<tr>
<td>18</td>
<td>allow for the identification and removal of barriers</td>
<td>“Strategic direction of complex organisations consists of establishing and modifying environments within which effective, improvised, self-organised solutions can evolve”.</td>
<td>AdjT.3.2</td>
</tr>
<tr>
<td>19</td>
<td>allow to determine the decidability and effective calculability of a proposed investigation</td>
<td><strong>Computability</strong> is the ability to solve a problem in an effective manner. This is closely linked to the existence of an algorithm to solve the problem.</td>
<td>AdjT.4.1</td>
</tr>
<tr>
<td>No</td>
<td>Refined (Low level) requirements</td>
<td>Theoretical insight</td>
<td>Adjuvant Theory</td>
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<tr>
<td>20</td>
<td>allow to determine the virtualisation of a proposed investigation</td>
<td>Process <strong>virtualisation</strong> theory proposes a set of constructs and relationships to explain and predict how suitable a process is to being conducted in a virtual environment.</td>
<td>AdjT.4.2</td>
</tr>
<tr>
<td>21</td>
<td>allow to determine the computational complexity of a proposed investigation</td>
<td><strong>Computational complexity</strong> computational difficulty of computable functions, i.e. the resources required during computation to solve a given problem. time (duration) and space (processing memory).</td>
<td>AdjT.4.3</td>
</tr>
<tr>
<td>22</td>
<td>enable systemic capacity building</td>
<td>Systemic capacity building, in terms of (1) structures, systems and roles, (2) staff and facilities, (3) skills, and (4) tools, would improve diagnosis of shortcomings in specific locations, improve project/programme design and monitoring, and lead to more effective use of resources.</td>
<td>AdjT.4.4</td>
</tr>
<tr>
<td>23</td>
<td>enable the formation of structured collaborations among pharmacovigilance stakeholder organisations to accommodate knowledge exchange processes</td>
<td>Organisational dependency on external resources affects their structure and patterns of behaviour to acquire and maintain needed external resources (forming collaborations, alliances, joint ventures, etc, or striving to overcome dependencies).</td>
<td>AdjT.5.1</td>
</tr>
<tr>
<td>24</td>
<td>enable disruptive innovation practices</td>
<td>Disruptive innovation: disruptive impact is caused by the business model that the technology enables</td>
<td>AdjT.6.1</td>
</tr>
<tr>
<td>25</td>
<td>enable absorptive capacity building in pharmacovigilance stakeholder organisations to accommodate knowledge exchange processes</td>
<td>Absorptive capacity of the organisation: ability to identify, assimilate, transform, and apply valuable external knowledge.</td>
<td>AdjT.6.2</td>
</tr>
<tr>
<td>26</td>
<td>enable the alignment of the information processing capability of pharmacovigilance stakeholder organisations with the information processing needs resulting from their involvement in pharmacovigilance innovations</td>
<td>Fitment between an organisation’s information processing needs and information processing capability is a determinant of performance</td>
<td>AdjT.6.3</td>
</tr>
<tr>
<td>27</td>
<td>enable dynamic capability building</td>
<td>Dynamic capability of an organisation to purposefully adapt their resource base. dynamic capabilities as ‘the ability to integrate, build, and reconfigure internal and external competencies to address rapidly-changing environments”</td>
<td>AdjT.6.4</td>
</tr>
<tr>
<td>28</td>
<td>enable the multi-level assessment of the value proposition of pharmacovigilance innovations</td>
<td>Technology must be analysed at two levels, the level of the original functional relation to reality and the level of design and implementation. The primary level simplifies objects for incorporation into a device while the secondary level integrates the simplified objects to a natural and social environment.</td>
<td>AdjT.6.5</td>
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</table>
Table 4.1: The Reference Framework

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</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>enable forward thinking and strategic planning to anticipate and accommodate pharmacovigilance innovations</td>
<td>Organisational foresight encompasses a range of approaches: (1) forecasting, forward thinking and prospectives (identify futures), (2) strategic analysis and priority setting (planning), and (3) dialogue and orientations (networking and agreement).</td>
<td>AdjT.7.1</td>
</tr>
<tr>
<td>30</td>
<td>enable collective creative design for pharmacovigilance innovation</td>
<td>Collaborative creativity methods build on four main dimensions: (i) explore the whole conceptual potential of the initial concept, (ii) involve and support people in a rule-breaking process, (iii) enable relevant knowledge activation, acquisition and production, and (iv) manage collective acceptance and legitimacy of rules (re)building.</td>
<td>AdjT.8.1</td>
</tr>
<tr>
<td>31</td>
<td>enable the analysis of the performance of pharmacovigilance innovation systems and processes</td>
<td>An information system can be evaluated in terms of information, system, and service quality.</td>
<td>AdjT.9.1</td>
</tr>
</tbody>
</table>

2.2 System design paradigms

The design, implementation, sustainance and optimisation of pharmacovigilance innovations is a reflective, iterative, interdisciplinary and participatory process that links knowledge (science) and action (practice), by combining, refining, interpreting and communicating knowledge within a socio-technical system. In the previous sections the characteristics of this process were discussed and systematised in the form of objectives and requirements. This section looks into relevant system design paradigms to accommodate these preconditions.

Simon (1996) described artefact design as a problem-solving activity. He argued that during the design activity, designers engage in iterative learning about both the problem space and the solution space. The present research, rather than accepting the limiting "bounded rationality" perspective for problem solving (focusing on existing paths), views knowledge discovery as a process "expandable rationality" (exploration of paths “in potentia”) that enables design for innovation (Hatchuel, 2001). Furthermore, the present research considers medicines safety investigations to be collaborative learning exercises (Engeström, 1999) taking the form of transactive memory systems. (Wegner et al., 1985; Wegner, 1987; Brandon & Hollingshead, 2004). Engeström's theory views learning as an expansive process: individuals question the accepted practices, and this initiates new learning cycles within the activity system. Transactive memory systems build on the notion of cognitive interdependence, i.e. individuals rely on each
other for being experts in certain knowledge domains and individual outcomes depend partially on what others in the group know.

In view of the analysis of requirements presented in the previous sections, with respect to system design paradigms, the Research Framework needs to take a horizontal approach spanning three main areas:

- **Research knowledge translation**: the transfer of research into practice (research use).
- **Systems engineering**: design and management of complex systems over their life cycles.
- **Collaboration and active knowledge exchange** in the form of **deliberative dialogue** among stakeholders that leverages individual knowledge and expertise, in order to find the best course of action at various stages of the process, including while initiating new learning cycles.

**Knowledge translation** (KT), also referred to as **knowledge utilisation, research transfer, or research utilisation**, describes the activities involved in moving research from the laboratory to practical use. It encompasses all steps between the creation of new knowledge and its application to yield beneficial outcomes for society (CIHR; 2004; Estabrooks et al., 2006; Graham et al., 2006; Straus et al., 2013). **Systems engineering** is an interdisciplinary field of engineering and engineering management that focuses on how to design and manage complex systems over their life cycles. Many implementation theories for promoting effective implementation have been described in literature (e.g. Moser, 2013). The systems engineering process is a **discovery** and a **maturing** process. A number of maturity models exist for ICT-centred innovation and development in general (Achi et al., 2016). The most commonly used and acknowledged maturity models are CMM and SPICE (ISO 15504). **Deliberative dialogue** is a collaborative process often employed for the purpose of informing policy development and can help to integrate and interpret scientific and contextual data (Culyer and Lomas 2006). In the case of pharmacovigilance innovation dialogue is deliberate and instrumental to the process of planning, organising, processing and reporting. Collaborative partnerships are characterised by interdependency, since none of the participants has enough autonomy or power to collect and translate the information into practices on their own. Individual participants are embedded in systemic relations, in which knowledge use is based on sense making (Nonaka 1994; Contandriopoulos et al., 2010). Selected frameworks from the aforementioned areas of interest are discussed bellow:
Chapter 4: The Reference Framework

2.2.1 Research translation

Analogies can be drawn from Translation of Research frameworks, applied primarily in the context of healthcare for the implementation of health services research findings into practice (Damschroder et al., 2009; Davidson, 2011). Several situated frameworks have been used to describe translation of research from basic to applied science in specific domains. One popular view of Knowledge Translation in the biomedical field is the categorisation of research into phases, broadly described as: (a) basic research, (b) methods development, (c) efficacy trials, (d) effectiveness trials, and (e) dissemination trials (Sussman et al., 2006). These models typically adopt a linear perspective and lack feedback loops. Other models approach translation as a two-category process. The first category, Type 1 translational research often is presented as the translation of basic or etiological research into intervention design (“bench to bedside”). It involves the use of basic or clinical findings to inform intervention development. The primary goal of Type 2 translation is to institutionalise a socially or personally relevant program (product or service), stemming from the concern that many clinical research discoveries never find their way into commonly accepted medical practice (Spoth et al., 2008). Glasgow et al. (2003) argued against rigid adherence to the five-phase model. In particular, they asserted that the five-phase linear perspective has led to a disconnection between efficacy and effectiveness research. Influences between basic and applied science can be bidirectional (Sussman et al., 2006). For example, a reciprocal and iterative process of using basic science discoveries to develop innovative prevention and treatment strategies is one direction of translation. Using discoveries from prevention and treatment research to develop new questions for basic science is the other direction of translation. Sudsawad (2007) provides an overview of a variety of generic Knowledge Translation models, including the Stetler Model of Research Utilisation (Stetler & Marram, 1976; Stetler, 1994, 2001), the Coordinated Implementation Model (Lomas, 1993), the Promoting Action on Research Implementation in Health Services (PARIHS) framework (Kitson et al., 1998; Rycroft-Malone et al., 2002 Rycroft-Malone, 2004; Kitson et al., 2008; Helfrich et al., 2010), the Ottawa Model of Research Utilisation (OMRU) (Logan & Graham, 1998), and the Knowledge to Action (KTA) process framework. An important characteristic of Knowledge Translation frameworks is that they are conceptualised as interactive, bi-directional processes, in which implementation informs further research. These are briefly outlined below:
(i) Stetler Model of Research Utilisation
The Stetler Model of Research Utilisation (Stetler & Marram, 1976; Stetler, 1994, 2001) is the practitioner-oriented model, designed to be used by individual practitioners as a procedural and conceptual guide for the application of research in practice. The model links research use, as a first step, with evidence-informed practice and consists of five phases (Stetler, 2001): (1) Preparation, (2) Validation, (3) Comparative Evaluation/Decision Making, (4) Translation/Application, and (5) Evaluation. Each phase is designed to: facilitate critical thinking about the practical application of research findings; result in the use of evidence in the context of daily practice; and mitigate some of the human errors made in decision making. The Stetler model of evidence-based practice proposes the following criteria to determine the desirability and feasibility of applying a study or studies to address an issue: (a) substantiating evidence; (b) current practice (relates to the extent of need for change); (c) fit of the substantiated evidence for the user group and settings; and (d) feasibility of implementing the research findings (risk/benefit assessment, availability of resources, stakeholder readiness).

(ii) Coordinated Implementation Model
The Coordinated Implementation Model (Lomas, 1993) outlines the overall practice environment to capture schematically the competing factors of influence to the implementation process. It states that the approaches used to transfer research knowledge into practice must take into account the views, activities, and available implementation instruments of the involved stakeholder groups (community interest groups, administrators, public policymakers, and clinical policymakers). This model acknowledges the significance of contextual factors that influence the Knowledge Translation process during the implementation phase.

(iii) Ottawa Model of Research Utilisation (OMRU)
The Ottawa Model of Research Use (Logan & Graham, 1998) views research use as a dynamic process of interconnected decisions and actions by different individuals relating to each of the model elements(Graham & Logan, 2004). Firstly, under the domain of “assess barriers and supports”, the proposed evidence-based innovation is examined in conjunction with the characteristics of potential adopters and the practice environment. This is followed by the implementation of interventions strategies (for barriers management, transfer and follow up) and the adoption of the innovation, under the “Monitor intervention and degree of use” domain.
Finally, outcomes resulting from implementation of the innovation are evaluated, under the “evaluate outcomes” domain. The model included feedback loops to the components under the assess barriers and supports domain, denoting an ongoing assessment of the barriers and supports under the light of information obtained later in the process.

(iv) **Knowledge to Action process framework**
The Knowledge-to-Action Process Framework (Graham et al., 2006) is a conceptual framework that could be useful for facilitating the use of research knowledge by several stakeholders, such as practitioners, policymakers, patients, and the public. The KTA process has two components: (1) knowledge creation and (2) action. Each component contains several phases. First, knowledge undergoes a process of synthesis to contextualise and integrate the findings of an individual research study, and to create knowledge tools (knowledge creation “funnel”). Subsequently, an action cycle is launched for the practical application of this knowledge.

(v) **Promoting Action on Research Implementation in Health Services (PARIHS) framework**
The PARiHS Framework, originally developed in 1998, is a widely used conceptual framework for guiding the implementation of evidence-based practices (EBPs). PARIHS proposes three key, interacting elements that influence successful implementation of EBPs: Evidence (E), Context (C), and Facilitation (F). Aim of the framework is to "provide a map to enable others to make sense of the complexity of implementation, and the elements that require attention if implementation is more likely to be successful" (Kitson et al., 2008). The PARIHS framework presents successful research implementation as a function of the relationships among evidence, context, and facilitation. The framework considers these elements to have a dynamic, simultaneous relationship. The proposition is that for implementation of evidence to be successful, there needs to be clarity about the nature of the evidence being used, the quality of context, and the type of facilitation needed to ensure a successful change process.

(vi) **CIHR's Knowledge translation model**
The CIHR's KT model (CIHR, 2004; 2005) offers a global picture of the overall KT process as integrated within the research knowledge production and application cycle. However, the use of other models and/or frameworks with more working details may be necessary to implement each part of the CIHR conceptual model successfully.
2.2.2 Information systems

According to Mora et al. (2003) a systems approach is a scientific paradigm suitable for the study of phenomena that are characterised by complexity, high level of interaction among their parts and the possession of properties that are lost when the whole phenomenon is considered partially isolated from its environment.

(i) Framework for IS Research

The Design Science Research theory (Hevner et al., 2004; Hevner, 2007) identifies three closely related cycles of activities in the process of IS design. The core activities of building and evaluating the IS artefacts and processes iterates between the relevance and the rigor perspective. The former links the design process with the actual application context to provide the design requirements and the acceptance criteria for the ultimate evaluation of the results. The latter looks at the current knowledge base to the research question addressed to ensure its innovation. DSR artefacts can broadly include: models, methods, constructs, instantiations and design theories, social innovations, new or previously unknown properties of technical, social or informational resources, new explanatory theories, new design and developments models and implementation processes or methods.
(ii) Systems development life cycle (SDLC)

The systems development life cycle (SDLC) is a conceptual model used in project management that describes the stages involved in an information system development project, from an initial feasibility study through maintenance of the completed application: planning, creating, testing, and deploying (Langer, 2008; Alter, 2008). The life-cycle of system development, as intended in the present research encompasses but is not limited to software development. Traditional software development methodologies, such as Waterfall method, V-Model and the Rational Unified Process (RUP), are based on a sequential series of steps. Agile development methods are based on the idea of incremental, spiralling and iterative development (Leau, 2012, Ruparelia, 2010).

2.2.3 ICT-centred innovation maturity models

In process management, the term "maturity" describes the degree of formality and/or optimisation of a given process. A maturity model is a management instrument designed to help organisations implement effective processes in a given management discipline (Simon, et al., 2010). A maturity model proposes a set of structured levels that describe how well the behaviours, practices and processes of an organisation can reliably and sustainably produce defined outcomes. Maturity models can be used as an evaluative basis for process assessment...
and improvement, assuming that higher process capability or organisational maturity is associated with increased effectiveness, control and better overall performance. It can further be used as a benchmark for comparative assessment of different organisations. There are various generic Capability/Maturity Models, including models specifically developed for the assessment of software processes.

(i) Capability Maturity Model (CMM)
Capability Maturity Model (CMM) version 1.1 is the most widely used maturity model. It was developed by the Software Engineering Institute, at Carnegie Mellon University (Curtis et al, 1993). Version 1.0 was released in 1991, following an initiative from the Department of Defence, which had identified the need for an assessment method of their software suppliers. Version 1.1 was released in 1993. CMM is a way to develop and refine an organisation's processes. The first CMM was for the purpose of developing and refining software development processes. A maturity model is a structured collection of elements that describe characteristics of effective processes. The CMM version 1.1 model is staged: each maturity level has a number of associated key process areas, denoting a cluster of related activities that, when performed together, achieve a set of goals considered important. Levels range from ad hoc implementations (level 1), to formally defined steps, to managed result metrics, to active optimisation of the software development process (level 5) (Hass, 2003). The latter represents the ideal state where processes would be systematically managed by a combination of process optimisation and continuous process improvement.

(ii) Capability Maturity Model Integration (CMMI)
Capability Maturity Model Integration (CMMI) is the successor of the capability maturity model (CMM). It was developed in an effort to improve the usability of maturity models by integrating many different models into one framework. CMMI thus is intended as a single model for organisations pursuing enterprise-wide process improvement. CMMI Version 1.1 was released in 2002, followed by Version 1.2 in 2006, and CMMI Version 1.3 in 2010. The model identifies three areas of interest: Product and service development — CMMI for Development (CMMI-DEV), Service establishment, management, — CMMI for Services (CMMI-SVC), and Product and service acquisition — CMMI for Acquisition (CMMI-ACQ), for which best practice documents (models) have been published. CMMI defines five maturity levels: (a) Initial; (b)
Managed; (c) Defined; (d) Quantitatively Managed; and (e) Optimising. The use of CMMI is complemented by the Standard CMMI Appraisal Method for Process Improvement (SCAMPI)(2011) a method developed by the Software Engineering Institute (SEI) to provide benchmark-quality ratings relative to CMMI models, namely to identify strengths and weaknesses of current processes, reveal development/acquisition risks, and determine capability and maturity level ratings.

(iii) ISO 15504 (SPICE)

SPICE (Software Process Improvement and Capability dEtermination) is the ISO 15504 standard for the assessment of the software development process and related business management functions. SPICE consists of 48 process areas each comprising results (outcomes) and corresponding best practices (Base Practices) as well as further information such as advice and work products. These process areas cover all important elements of IT product development, they are ordered into different categories and are complementary. For each SPICE process area a defined Capability Level can be achieved. The process model, including all process areas for SPICE, is shown in Figure 16.

![Figure 16. SPICE Process Area Model](source: Hass (2003))
Chapter 4: The Reference Framework

SPICE operates with six maturity levels: “incomplete”, “performed” “managed”, “established”, “predictable” and “optimising” process (Hass, 2003). The model provides achievable improvement steps, organised in reasonable sequence, for which immediate improvement priorities can be defined and progress can be measured. For instance, one of the attributes at level 2 (“managed process”) is work product management. This means that for any given process area to obtain level 2, all relevant work products from the performance of the process area must be placed under configuration management.

2.2.4 TranSTEP model for interdisciplinary learning and collaboration

The Trans Domain Technology Evaluation Process (TranSTEP) (Forsberg et al., 2014) was developed by the European research project EST-Frame. Intended as a conceptual guide for practical work, TranSTEP is an approach to the assessment of technologies or technological applications that present challenges related to complexity, uncertainty and controversy over facts and values. In such situations the legitimacy of any assessment may be challenged with respect to its input (who participates), throughput (how is the assessment conducted) and output (the quality of the result). TranSTEP focuses on the enhancement of communication and interdisciplinary learning between different domains of expertise, addressing the problem of expertise fragmentation, which is one of the main barriers to integrate factual evidence, values and normative perspectives across domains. The process is focused on creating permanent learning processes among participants. Firstly, a TranSTEP group for dialogues across institutional and disciplinary domains is convened. Their tasks include collaborative analysis of the situation (initial problem formulation) and problem framing, to be followed by reflection on possible methods for addressing the problem, and the review of existing evidence (previous assessments). The outcome could be a decision for new assessments to be carried out in order to fill knowledge gaps to provide answers to the problem, in case no suitable assessments exist. The process ends up in results integration, when robustness and legitimacy of outputs has been achieved. The model acknowledges the need for continual reflection and dialogue to adapt to the situation under scrutiny, and fill potential knowledge gaps identified. Its output is an original trans-disciplinary assessment, developed through dialogue between people involved in earlier assessments, in interaction with problem owners and other stakeholders (decision-makers, the public, etc.). This basic conviction in TranSTEP implies that situation analysis and method
reflection cannot be done as routine based actions. An advantage of the ad hoc nature of each TranSTEP process is that there is a very explicit focus on situation analysis and methodological deliberation. As the range of participants widens, the assessment process itself is made transparent and the output is subject to broad review. In this respect TranSTEP is conducive to better robustness and legitimacy of the output.

Figure 17. The TranSTEP process model [source: Forsberg et al. (2014)]

3. Discussion

Many model related to knowledge translation are reported in literature (Glasgow et al., 1999; Straus et al., 2009; Straus et al., 2013; Harvey & Kitson, 2015). Their scope varies, with the majority of these strategies focusing on implementation planning, namely, on the dissemination and practical implementation of existing research knowledge (knowledge to action). Knowledge translation models build on a combination of process and impact theories, with actions addressing issues of intervention implementation, individual adoption/uptake and maintenance for sustained use. Typically, actions included in knowledge translation models revolve around problem identification, selection of evidence-based process, review of fitment to the application context and identification of barriers, customisation, development of plan of intervention, translation/application, and evaluation. Strategies involving knowledge creation are included in a few models. The Knowledge Translation models presented in Section 2.2 are indicative of this variety, and while in their entirety none can meet the requirements set for the pharmacovigilance Reference Framework, each provides valuable partial insights (Table 22).
Table 22. Knowledge Translation models

<table>
<thead>
<tr>
<th>Knowledge Translation model</th>
<th>Scope</th>
<th>Learnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stetler Model of Research Utilisation</td>
<td>utilisation-focused knowledge to practice (process theory)</td>
<td>Dimensions of comparative evaluation</td>
</tr>
<tr>
<td>Coordinated Implementation Model</td>
<td>knowledge to practice</td>
<td>Holistic investigation of the practice environment</td>
</tr>
<tr>
<td>Ottawa Model of Research Use</td>
<td>knowledge to practice</td>
<td>Assessment, monitoring, and evaluation process</td>
</tr>
<tr>
<td>Knowledge-to-Action Process Framework</td>
<td>Knowledge-to-Action</td>
<td>Complex and dynamic process; No definite boundaries between knowledge creation and action; Collaboration between knowledge producers and knowledge users; Successful implementation of EBPs is influenced by three key, interacting elements: Evidence, Context, and Facilitation map for sense making</td>
</tr>
<tr>
<td>PARIHS framework</td>
<td>knowledge to practice</td>
<td>Successful implementation of EBPs is influenced by three key, interacting elements: Evidence, Context, and Facilitation map for sense making</td>
</tr>
<tr>
<td>CIHR's KT model</td>
<td>global KT model</td>
<td>Detailed depiction of the research knowledge production and application cycle; KT opportunities;</td>
</tr>
</tbody>
</table>

The Stetler Model (Stetler & Marram, 1976; Stetler, 1994, 2001) identifies four criteria for determining whether it is desirable to use the validated evidence in the practice setting (Phase III, comparative evaluation). These include: (a) *Substantiating evidence* is meant to recognize the potential value of both research and additional non-research-based information as a supplement; (b) *Fit of setting* refers to how similar the characteristics of the sample and study environment are to the population and setting of the practitioner; (c) *Feasibility* entails the evaluation of risk factors, need for resources, and readiness of others involved; and (d) *Current practice* entails a comparison between the current practice and the new practice (that may be introduced) to determine whether it will be worthwhile to change the practice. The Coordinated Implementation Model (Lomas, 1993) emphasises the role of the practice environment, proposing a holistic investigation, in order to identify the competing factors of influence to the implementation process. Areas investigated include: the administrative environment (regulation), the economic environment (incentives), the community environment (public pressure), and personal (catalysts), viewed under the light of relevant external factors. The Ottawa Model of Research Use (Logan & Graham, 1998) proposes a dynamic process of interconnected decisions and actions, involving (a) (barrier) assessment conducted on the proposed evidence-based innovation,
on its potential adopters and on the practice environment; (b) implementation of interventions and continuous monitoring of their adoptions and (c) evaluation of outcomes. The Knowledge-to-Action Process Framework (Graham et al., 2006) views Knowledge-to-Action as a complex and dynamic process, with no definite boundaries between knowledge creation and action and emphasises the collaboration between knowledge producers and knowledge users. The “action cycle” of knowledge application is a dynamic process in which all phases in the cycle can influence one another and can also be influenced by the knowledge creation process. The PARiHS Framework (Kitson et al., 1998) proposes three key, interacting elements that influence successful implementation of EBPs: Evidence (E), Context (C), and Facilitation (F). Aim of the framework is to "provide a map to enable others to make sense of the complexity of implementation, and the elements that require attention if implementation is more likely to be successful". The CIHR model (CIHR, 2004; 2005) offers a global picture of the overall Knowledge Translation process as integrated within the research knowledge production and application cycle. CIHR identified six opportunities within the research cycle at which the interactions, communications, and partnerships that could occur will help facilitate Knowledge Translation.

Maturity models are management instruments, founded on the acknowledgement that instantiated processes can be incomplete or imperfect. They entail the notion of value and propose process improvement, as a means to achieve the “optimum”. Maturity models are developed on the basis that organisations and processes progress along a journey of maturity, i.e. they do not move from zero to optimum capability instantaneously (Murray & Ward, 2007). Process improvement is a critical aspect of pharmacovigilance systems.

The TranSTEP model captures another important dimension of the innovation process. A pharmacovigilance investigation transcends different domains of expertise and authority. Interdisciplinary learning, through dialogue between work teams and between stakeholder organisations, is imperative for the consolidation of the various perspectives that exist within a study context and the alignment of capabilities towards the common objective. The model implies that situation analysis and method reflection cannot be viewed as routine actions. In the case of pharmacovigilance innovation dialogue is deliberate and instrumental to the process of planning, organising, processing and reporting.
From this analysis, it becomes evident that a global Knowledge Translation model is more aligned with the needs of pharmacovigilance. While the CIHR model provides a good overview of the research translation landscape, it lacks the sophistication and granularity required to accommodate the specific requirements of the pharmacovigilance domain, particularly with regards to research utilisation. Questions of implementation maturity and stakeholder collaboration, which, according to the analysis are integral to pharmacovigilance processes, are not addressed explicitly by any model. Recognising the multidimensional and complex nature of pharmacovigilance, and the current lack of a holistic overview, the present research cannot use a partially relevant Knowledge Translation framework as its staring point, since the meaning of Research Translation in the field of pharmacovigilance needs first to be determined. For this reason, the present inquiry adopted an inductive approach that is grounded in data, informed by theory to extract the requirements, which combined with learnings from the Knowledge Translation models studied and the principles of IS Research will produce a Reference Framework for pharmacovigilance innovation. The resulting Knowledge Discovery Cube Framework (KDC Framework) is discussed in detail in the following section (Part B).
Part B: The Knowledge Discovery Cube Framework

“The formulation of a problem is far more often essential than its solution, which may be merely a matter of mathematical or experimental skill. To raise new questions, new possibilities, to regard old problems from a new angle requires creative imagination and marks real advance in science.”

Albert Einstein & Leopold Infeld (1938)

1. Introduction
This section presents the proposed Reference Framework for collaborative, information-driven medicines safety investigations, detailing the concepts and their interrelationships. The KDC Framework includes constructs from a synthesis of existing theories and provides an overarching typology for medicines safety investigations. The early version of the framework was derived from a thorough review of the literature spanning several areas and from the author's' experience, as described in the previous sections. The final version of the Framework is detailed in the following sections.

2. About the “Knowledge Discovery Cub” Framework
The main challenge we have identified is that, although technology is advancing at a rapid pace, the adoption of innovation for drug safety monitoring is rather slow. There is a gap between value discovery and value realisation. We argue that while the investigation process is inherently knowledge intensive, relying upon the identification and application of rigorous, state-of-the-art scientific methods and technologies for evidence elicitation, relevance to the actual application context needs to be ensured, in order to achieve value. The implementation of the knowledge discovery process involves four distinct components (“People”, “Technology”, “Task”, “Organisation”). An in-depth investigation of the socio-technical ramifications of knowledge discovery is imperative, in order to develop effective work processes for knowledge extraction in real-life situations. In a given socio-technical context, safety monitoring mechanisms apply relevant investigation methods on available information sources supported by socio-technical capabilities, to achieve value. According to our investigation of relevant scholarly outcomes and empirical findings, the analysis dimensions to be considered during the design of a Smart Investigation Environment for a given RQ comprise: the scope and methods of the investigation,
the information sources available, the existing socio-technical capabilities and their limitations. The combined investigation of these dimensions allows assessing the value proposition of an investigation instance (investigation implementation). The resulting evidence creation processes are workflows combining technologies with human-lead processes. The proposed framework for the design of a Smart Investigation Environment for the investigation of any safety monitoring question is titled “Knowledge Discovery Cube” and is illustrated in Figure 18.

The proposed design and evaluation framework was developed after a critical appraisal of the existing findings of relevant theories, frameworks and empirical studies. It makes use of socio-technical systems theories to distinguish and interlink the analysis dimensions and measures.

![Figure 18: Knowledge Discovery Cube](image)

The feasibility and effectiveness of the RQ investigation process stand at the core of the analysis framework, which starts from the available knowledge sources and leverages technology and cutting-edge tools to advance the investigation, while balancing the environmental/organisational dimensions. Critical questions to be addressed include while designing a drug safety investigation include:
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Table 23. Feasibility and effectiveness investigation dimensions

| I: Is the investigation doable? (Sociotechnical Capabilities) |
| Are the basic conditions for the implementation of the investigation being met? |
| Are all the required sociotechnical capabilities available? |

| II: Is the output meaningful? (Attainable Benefit) |
| Is the evidence produced meaningful for the targeted stakeholder group? |

| III: Does the investigation add value? Is it cost-effective? (Attainable Benefit) |
| Is the value/cost ratio in maintaining and performing the investigation improved (i.e. greater cost effectiveness)? |

The primary scope is to examine and ascertain the feasibility of the investigation design blueprint (protocol) and to verify that it has the potential to be used for generating evidence on potential risks of medicines. For the purposes of the investigation of a RQ (scope) in a given context, attainable, relevant Knowledge Items are combined, which require and make use of the available relevant socio-technical capabilities to achieve value (attainable benefit).

Capabilities represent contextual, situational factors that affect information-driven medicines safety investigations, by conditioning performance capacity and actions.

A review of the literature reveals that currently, there is no single general reference point for the capabilities that affect medicines safety investigations, however, there are a number of different domains that have strong associations. We therefore construct an initial reference framework of the capabilities (situational factors) affecting information-driven medicines safety investigations, incorporating a range of related domains, informed by empirical evidence.

The workflow of a typical investigation process is depicted in Figure 19. Investigation objectives are mapped on the appropriate evidence sources and study methods. Required capabilities are identified and all is consolidated in the form of an investigation protocol. The protocol is subsequently implemented through the mobilisation/adaptation of relevant available capabilities (technical infrastructure and tools, organisational structure, people etc), producing an investigation system, i.e. an investigation instance. An instantiation is the realisation of an artefact in its environment. The study is executed yielding investigation results, the evaluation of which (and of the process as a whole) serves for the review and improvement of the investigation.
Chapter 4: The Reference Framework

A Research Investigation thus represents an iterative process of continual improvement that features
- incremental improvements within the existing process, based on the analysis and evaluation of the obtained results (plan–do–check–act, Deming, 2000);
- discontinuous or breakthrough improvements, e.g. as a result technology innovations, that create new dimensions of performance and value (Veryzer, 1998).

3. Concepts

March & Smith (1995) define constructs or concepts as the vocabulary of a domain, a “conceptualisation used to describe problems within the domain and to specify their solutions”. They form the specialised, standardised language and shared knowledge of a discipline or subdiscipline. Concept descriptions are constructed from concept properties (features, dimensions) (Smith & Medin, 1981). For the purposes of developing the KDC Framework, existing terminology and constructs from relevant theories have been reviewed. The resulting vocabulary builds on and combines concepts across theories to develop concise, yet generic, definitions that can be readily operationalised for the development and implementation of any Research Investigation in any given socio-technical context. Table 24 summarises the principal concepts included in the KDC Framework.

<table>
<thead>
<tr>
<th>Concept</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Investigation</td>
<td>The design and implementation of dedicated studies targeting medicines safety issues or involving medicines safety data.</td>
</tr>
<tr>
<td>Protocol</td>
<td>“Protocol” is a formalised procedural method in the design and implementation of studies.</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Concept</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data</td>
<td>“Data” refers to data evidence employed in the investigation, i.e. all specified sources of information relevant to a specific research investigation.</td>
</tr>
<tr>
<td>Tasks</td>
<td>“Tasks” refer to all the tasks and subtasks involved in executing a Research Investigation (study protocol or tentative study plan).</td>
</tr>
<tr>
<td>Capabilities</td>
<td>“Capabilities” represent contextual, situational factors that affect information-driven pharma safety investigations, conditioning performance capabilities and actions. Capabilities span the social and technical domain, they can be tangible (e.g. physical artefacts) or intangible (e.g. organisational culture) and relate to the people involved, the tasks performed and the technological means employed.</td>
</tr>
<tr>
<td>Technology</td>
<td>“Technology” refers to all the equipment and machinery required for the execution of tasks: Infrastructure and tools spanning the entire digital knowledge value chain: data collection &amp; reporting tools, data storage, retrieval &amp; transfer infrastructure, Data &amp; Text mining tools, Computational tools, Decision Support tools, communication &amp; collaboration tools, Knowledge Management tools</td>
</tr>
<tr>
<td>People</td>
<td>“People” refers to people as actors, performing work as part of the RI People actively involved in some stage of the investigation (issues: knowledge, skills, motivation)</td>
</tr>
<tr>
<td>Structure</td>
<td>“Structure” comprises the authority structure, communication and collaboration channels, and workflow within and among participating organisations. Governance structures, systems, and roles, Policy and legal provisions, guidelines</td>
</tr>
</tbody>
</table>

The principal concepts are detailed below:

3.1 Research Investigation

We define Research Investigations (RIs) as the design and implementation of dedicated studies targeting medicines safety issues or involving medicines safety data. RIs represent research and development interventions that address specific Research Questions (RQs) revolving around medicines safety. Pharmacovigilance is a knowledge ecosystem that is open to its environment. With regards to Research Investigations this implies that investigations may build on or serve the knowledge needs of both internal and external stakeholders; may exploit technological
innovations and opportunities, and re-frame knowledge stemming from within “traditional” pharmacovigilance or from external domains. From a scientific perspective, progress can be viewed as "development-by-accumulation" or as episodic (disruptive) (Kuhn, 1962). RIs may follow established paths (i.e. build on scientifically proven methods and protocols) or seek to explore paths “in potentia” (i.e. new research directions) (Robinson & Propp, 2008; Agogué et al., 2012). RQs may build on well-defined methods (existing paths), which may be further improved through the assimilation of technology innovations and information sources. Paths ‘in potentia’ essentially represent cutting edge research aiming to generate new insight, develop protocols and apply them in practice. Agogué et al.(2012) distinguish paths ‘in potentia’ into (1) concepts that exist as unexplored pathways in the current known space of the innovation field and (2) concepts that exist as unexplored pathways in the unknown areas of the innovation field. They note that paths-in-the-unknown, i.e. paths that have not been developed or explored to date, can only be explored by expanding the innovative capabilities of the actors for reasoning in the unknown (Table 25).

**Table 25. Investigation paths [Source: Agogué et al.(2012)]**

<table>
<thead>
<tr>
<th>Denomination</th>
<th>Description capabilities</th>
<th>Innovation assessment</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Existing paths</td>
<td>Known paths</td>
<td>Product of the existing innovation capabilities</td>
<td>Known value</td>
</tr>
<tr>
<td>Path-in-potentia</td>
<td>(1) Attainable paths</td>
<td>Attainable with a re-combination of existing capabilities</td>
<td>Forecasted value</td>
</tr>
<tr>
<td></td>
<td>(2) Path-in-the-unknown</td>
<td>Attainable with new innovation capabilities</td>
<td>Unknown value, high uncertainty</td>
</tr>
</tbody>
</table>

Research innovation can be combinatorial, exploratory or transformational, supported by simple, complicated or complex research designs (protocols). Viewed as a discovery process, a Research Investigation is essentially about generating something new that has value. As such it can further be described as a **creative process** (Higgins, 1994). Building on the paradigm of creative information exploration for the generation of creative insight and solutions (Boden, 1994; Dubitzky et al., 2012), a Research investigation can be characterised as:
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- **Combinatorial**, creating unfamiliar combinations of familiar concepts and constructs, i.e. uncovering, selecting, combining and synthesising existing information, concepts and methods to create a new “whole” (Koestler, 1964);
- **Exploratory**, pursuing the discovery of so far unknown possibilities, on the basis of examining new possible combinations of the elements of the drug safety conceptual space (e.g. Swanson linking, (Swanson, 1989));
- **Transformational**, challenging the established assumptions and reasoning of the conceptual space, to attempt to think what is unthinkable.

Typically a RI is conceptualised as a simple, linear process, however this is seldom the case, as investigations involve complicated and/or complex aspects, which need to be identified and addressed. Complicated processes are essentially predictable, although they involve multiple components and require expertise in each component to bring the components together effectively, since the all components are known. Complex processes are emergent, adaptive and responsive and are inherently unpredictable since they revolve around unknown concepts, generating relevant knowledge as they go (Glouberman & Zimmerman, 2002). For example research investigations spanning several information areas can be regarded as complex. Peersman et al. (2016) provide the following description of the meaning of simple, complicated and complex aspects in the context of healthcare interventions (Table 26).

**Table 26. Characterisation of interventions [source: Peersman et al. (2016)]**

<table>
<thead>
<tr>
<th>Simple, ‘known’</th>
<th>Standardised</th>
<th>Knowledge transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>– <em>a single way to do it</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Works pretty much the same everywhere/for everyone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Best practices can be recommended confidently</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complicated, ‘knowable’</th>
<th>Adapted</th>
<th>Knowledge translation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>– <em>need to do it differently in different settings</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Works only in specific contexts that can be identified</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Good practices in particular contexts</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complex, ‘unknowable’</th>
<th>Adaptive</th>
<th>Ongoing knowledge generation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>– <em>need to work it out as you go along</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dynamic and emergent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patterns are only evident in retrospect</td>
<td></td>
</tr>
</tbody>
</table>

From a system’s point of view Research investigations and can vary in terms of **maturity**: A research investigation can be exploratory or an established investigation practice. Described
based on the ISO 15504 (SPICE) standard for software process assessment, an exploratory investigation may result in a Level 0 (incomplete process) or a Level 1 (Performed Process) maturity. An established investigation practice corresponds to higher levels of maturity.

Managing RIs as an alignment process
A RI can further be conceptualised as a **strategic planning and alignment exercise** that follows a strategic cascading path (Figure 20), meaning that strategic elements at high-level (Research Questions) are translated into lower level objectives that support strategy, are linked to specific investigation methods and data inputs and then translated into tasks, activities and other capabilities that need be in place for the RI to be successfully implemented. Alignment is defined as bringing key elements into proper coordination, agreement, and close cooperation.

Building on the notion of balanced scorecard (Kaplan & Norton, 1996a), a methodology for strategic planning and management that enables organisations to clarify their vision and strategy and translate them into action: align business activities to the vision and strategy of the organisation and monitor performance against strategic goals, we construct a strategy map (Kaplan & Norton, 1996b; Flood et al., 2000; Lawrie & Gobbold, 2004) for Research Investigations.

![Figure 20. Levels of analysis of a Research Investigation](image)

The implementation of a RI delving into the unknown can start as a flexible direct enactment, achieve to deduct descriptive pattern support and prescriptive pattern support, from which to produce a strict protocol model for the RQs at hand. The **RI Protocol** represents a formalised
procedural method in the design and implementation of Research Investigations, outlining, coordinating and standardising all the elements of the RI across and within all participants. The protocol may be tentative (provisional and subject to review and refinement), in the case of exploratory RIs, or standardised, in the case of established investigation practices. The RI defines and details the Objective(s), the scientific method and the data sources to be used as evidence, which are subsequently mapped on required capabilities during implementation. Different sets of capabilities may apply for different data evidence. The high-level Research Questions are translated into a set of objectives $O_1,...,O_m$:

$$O = \{O_1,...,O_m\}$$

That are operationalised in the form of a RI protocol ($P_{RI}$), which is a function of the scientific method ($M$) and the data sources utilised ($D_1,...D_n$).

$$P_{RI} = F\{M, D_1,...D_n\}$$

The answers to the Research Question(s) of the RI may be derived from the aggregation or the orchestration of individual Objectives. To facilitate the analysis work, the number of objectives set ($m$) should exceed the number of data sources ($n$): $m \geq n$. Specific objectives should be defined for individual data sources.

The RI protocol represents the blueprint of the investigation. Its aim is to explain and specify “how” (top-down direction) the RI is performed: how based on the selected study method, appropriate data evidence can be located and mobilised effectively through the alignment of all required environmental conditions (capabilities).

### 3.2 Value

The capacity of a method to produce valid and useable outcomes is conditioned by the availability of quality evidence (data sources) and appropriate supporting capabilities, including the effective working of the knowledge value community (work processes).

**The attainable Benefit of a** Research Investigation (**Value of the RI**) is defined as a function of the method selected, the data source(s) employed for the investigation, and the supporting capabilities available.

$$V_{RI} = F\{M; D_1,...D_n; C_1,...C_n\}$$
Together with the strength of the scientific method, the availability of data evidence of value and the alignment of the situational factors (capabilities) represent the key determinant of the attainable Benefit of a RI. Depending on the case, the obtained benefit (realised value) can be determined from different perspectives, e.g. scientific validity of the output of the RI, quality of the investigation, use of information and communication infrastructure, stakeholder satisfaction etc). Three degrees of value can be distinguished:

- **Realised value** refers to the actual value achieved by the RI investigation (actual capabilities and methods employed).
- **Probable value** refers to the optimal value achievable through the application of the most rigorous consolidated methods at the time (use of consolidated state-of-the-art technologies and tools, availability of all relevant knowledge sources, successful organisational alignment etc).
- **Potential value** refers to the value proposition of emerging technology innovations and/or organisational and regulatory change.

The difference between the realised value of a Research Investigation and its probable value denotes the existence of a performance gap, i.e. that the RI instance failed to achieve its full potential and requires improvement. The difference between probable and potential value signals an innovation gap, i.e. potential benefit to be obtained through the consolidation and mainstreaming of emerging innovations (Figure 21).

![Figure 21. Analysis scheme for value assessment](image)

In a constantly evolving technology environment, technology innovation represents the principal area from which added value can be drawn (e.g. advances in data mining technologies).
However, the potential of new methods in real-life may be conditioned by organisational or regulatory limitations, in which case the value potential of new technologies can only be achieved through structural or legal change. The systematic organisation and structuring of all the elements of the RI allow measuring the achieved benefit (top-down direction) and also to ask “what if” questions (bottom-up direction) and assess the expected added value of potential improvements and innovations. In this manner, the identified models of innovation valorisation (Table 19) can be accommodated.

3.3 Data
Starting point of a Research Investigation is to integrate existing knowledge that is compatible with the problem formulation (Objective(s)) and the selected method into an evidence base for responding to this problem. Data (evidence) for safety investigation purposes may be drawn from all types of sources, be they patient level data or formal records. Data of value to a RI is usable data. A preliminary assessment of the suitability of data sources needs to be undertaken during investigation planning. Organisers need to select the most appropriate sources of evidence with regards to fitment for purpose, quality and availability.

A Research Investigation requires data that is fit for purpose, i.e. data of relevance to the scope of the investigation and also of sufficient quality in terms of accuracy, timeliness, consistency, and completeness (Wand & Wang, 1996; Wang & Strong, 1996; Strong et al., 1997, Pipino et al., 2002; Lee et al., 2002). Assurance of trust in data evidence is paramount. Furthermore, data needs to be available, i.e. not bound by accessibility restrictions, due to legislation or data custodian imposed limitations (data governance rules). Data governance issues need to be evaluated and resolved at the onset of a Research Investigation. Changes in legislation or in organisational policies may result in fundamental shifts in what can be done with specific data. Consequently, availability will have to be reassessed. Specific purpose-related data partnerships may be set up to create permanent exchange channels for established investigation practices.

From the data exchange perspective, commitment to FAIR principles (Findable, Accessible, Interoperable, Reusable) is required (Wilkinson et al., 2016). In line with the Objectives and the study method of the Investigation, data evidence needs to be located, collected, evaluated, assembled and processed to yield the respective Objectives, produce insight regarding the respective Research Questions and inform decisions and actions.
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Extending the evidence base of pharmacovigilance implies the combined use of “traditional” pharmacovigilance data (from SRSs, registries etc) and new data channels (e.g. social media data). A further diversification is that data can be structured or unstructured. Deriving value from diverse knowledge sources requires unifying unstructured content & data with structured data in a way that allows end-users to gain deeper insights than possible with analysis of structured data alone. There are a number of scenarios in which new data sources could be used in pharmacovigilance investigations. Table 27 proposes a taxonomy of new data evidence utilisation cases, developed as part of the present analysis.

Table 27. Taxonomy of new data evidence utilisation cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case I</td>
<td>New data sources used as auxiliary information to improve all or part of an existing investigation that builds on traditional data channels;</td>
</tr>
<tr>
<td>Case II</td>
<td>New data sources supplement/replace all or part of an existing investigation with data from new channels;</td>
</tr>
<tr>
<td>Case III</td>
<td>New drug safety insight is produced solely based on new data sources;</td>
</tr>
<tr>
<td>Case IV</td>
<td>New investigations are conducted that combine data from traditional and new sources.</td>
</tr>
</tbody>
</table>

For example, consulting social data as an additional reference during the deliberation stage of statistical SRS signal processing would fall under Case I. Using social data metrics to decide whether ADR reports collected in a SRS need further investigation would fall under Case II. Social data replacing SRS, would fall under Case III, meaning social data are a sufficient source of insight for signal detection. Developing a new method that relies on both reported ADR and social data-extracted information as input for signal detection, would fall under Case IV.

Data is generated from several sources, including the SRS process, industry, patients, and healthcare professionals. Data evidence is produced continuously. RIs examine either a fraction of this data in retrospect or incoming data in real time. The selection of an investigation method is closely interlinked with the intrinsic characteristics and limitations of the different data sources employed, which also determine the underlying capabilities required to perform the investigation. The term “data lanes” is used to refer to the different streams of data employed in an investigation, defined according to their type, e.g. structured data (from databases), unstructured data (from social media) etc. A RI may combine data from different data lanes.
Data sources can be either internal or external to the organisation that instigates the RI. Studying the effects of task complexity on information seeking and found in a public administration context, Byström and Järvelin (1995) found that, as task complexity increases, the complexity of information needed, the needs for domain information and problem solving information, the share of general-purpose sources (experts, literature, personal collections), and the overall number of sources increased, while the share of problem and fact-oriented sources, the success of information seeking, and the internality of channels decreased.

### 3.4 Capabilities

For the purposes of an investigation of a RQ (scope) in a given context, attainable, relevant Knowledge Items (data evidence) are aggregated and combined, according to appropriate study methods which require and make use of the available relevant socio-technical capabilities to achieve value (attainable benefit). In business terms, capabilities denote an organisation's capacity to engage in a range of productive activities. All organisations possess unique bundles of resources, and it is how these resources are used that determines differences in performance between organisations. Resources are not productive in themselves – they need to be converted into capabilities by being managed and coordinated (Grant, 1998). The Business Dictionary describes organisational capabilities as the ability and capacity of an organisation expressed in terms of its (1) Human resources: their number, quality, skills, and experience, (2) Physical and material resources: machines, land, buildings, (3) Financial resources: money and credit, (4) Information resources: pool of knowledge, databases, and (5) Intellectual resources: copyrights, designs, patents, etc. Capability thus models what a business function does, i.e. its externally visible behaviour, and the expected level of performance. According to Gieskes and Langenberg (2000), capabilities are integrated resources that the organisation deliberately draws together. These resources include tangible and intangible assets ranging from behaviours and skills to information systems.

**In the present context, capabilities represent contextual, situational factors that affect information-driven medicines safety investigations, conditioning performance capabilities and actions.** Capabilities span the social and technical domain, they can be tangible (e.g. physical artefacts) or intangible (e.g. organisational culture) and relate to the people involved, the tasks performed and the technological means employed. Acknowledging the complexity of the
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implementation of change in organisations, Leavitt (1965) proposed the analysis of organisations using a four-dimensional diamond, featuring Task, Technology, People, and Structure as interrelated and mutually adjusting variables. In the case of IT innovation, when designing a technical solution, an integrated view over all dimensions is required, so as to understand their interdependencies and plan the implementation process accordingly. Leavitt’s diamond provides an integrated view on the forces at play in organisations. Leavitt argued that when one dimension is changed, the impact of the innovation is often balanced by the other components (compensatory or retaliatory change). Consequently, while planning a change, a holistic examination of all aspects is required. Similar classifications of factors have been adopted in other areas, including healthcare. For example in its Blueprint for telemedicine deployment in Europe, the MOMENTUM project (Kvistgaard Jensen et al., 2015) identified factors falling within four categories (context, people, plan and run), which included the need to involve stakeholders and account for actual needs, guarantee the legal security of the health records and the need to set up a proper management and business plan. The Telehealth Capacity Assessment Tool (Waters et al., 2013) assesses factors from six key domains (Organisational Readiness, Technology, Regulatory and Policy, Financing and Reimbursement, Clinical and Workforce), which have been shown to complement and reinforce each other, and together combine to enhance the implementation, quality, integrity, sustainability, and impact of telehealth initiatives. Similarly, the implementation of a RI is conditioned by both organisational and operational enablers. The former broadly refer to the overarching organisation structures, governance, collaboration etc and the way these affect the RI. The latter includes the processes, tools, technologies and personnel needed to implement the RI. For the purposes of the KDC Framework we categorise capabilities into technologies-, people-, and organisation-related factors.

- **Technology**: includes all the equipment and machinery required for the execution of tasks.
- **People**: refers to people as actors, performing work as part of the RI
- **Structure**: comprises the authority structure, communication and collaboration channels, and workflow within and among participating organisations.

A RI is essentially a Knowledge Management exercise that builds on knowledge contained in both **information sources** and **people**. Capabilities therefore need to be examined from both
perspectives, as they entail both an information management and a behavioural aspect. The first perspective builds on the notion of knowledge as an object that can be captured and transferred. The second views KM as a collaborative knowledge creation process that is unique to each individual. Organisational and operational enablers are critical for the extraction of knowledge from informational assets and for collaborative knowledge creation. Capabilities are closely interlinked with the data evidence employed, the investigation methods and the corresponding tasks (i.e. all the tasks and subtasks involved in executing a Research Investigation based on a concrete study protocol or a tentative study plan). They should also facilitate the just-in-time availability and efficient diffusion of expertise, through the accessibility and partnering of knowledge carriers (Pappa et al., 2009), the key challenges of information integration, knowledge sharing, and connectivity between people, so as to facilitate the sharing and use of unarticulated knowledge.

Capabilities represent critical success factors. They are necessary for a RI to achieve its mission, being the elements that can drive an investigation strategy forward and make or break the success of the investigation. An in-depth understanding of capabilities is essential during the design and implementation (operationalisation) of a RI. For this purpose, capabilities are defined on the data stream level, in order to best capture the diverging needs of the different data sources, and can be further detailed on the individual organisation level, to guide local planning (local situational factors). Participating organisations should balance their capabilities against the requirements stipulated by their role in the RI (e.g. information generation/aggregation, information-processing).

The implementation of a RI (investigation system or investigation instance) can be sequential, evolutionary (iterative) or incremental. In the first case a strictly delineated order of execution is applied, as all artefacts are well specified. In the evolutionary instantiation, the implementation is characterised by uncertainty, which results in iterations and the revision of provisional configurations. In each cycle the system is improved by solving problems discovered in a previous cycle. Incremental instantiation is a combination of the two life-cycles.

4. The Research Investigation life-cycle model

In the previous sections of this chapter the typical application scenario was discussed. The core mission of the Reference Framework is the digitisation and operationalisation of known
methods, the development/discovery of new methods, and the improvement and optimisation of instantiated investigations. Instantiations operationalise constructs, models, and methods. Aim of the KDC Framework is to delineate causal and explanatory relationships and establish practical references to facilitate the incorporation of emerging domain knowledge and technological innovation. In this context, the principal innovation triggers in drug safety investigations are **advances in technology**, which generate and allow access to new sources of evidence and improve data processing and insight generation processes. However, this is not a one-way process moving from technology innovation to drug safety innovations, but a **reciprocal process of interaction and exchange**, with requirements collected and lessons learned during the instantiation leading to process improvements or influencing subsequent rounds of research.

Furthermore, as highlighted by Kaplan & Orlikowski (2014), **new visions of the future** trigger reconsiderations of current concerns, as future projections are intimately tied to interpretations of the past and the present. The past, present and future are thus all interpreted and reinterpreted continuously. The KDC methodology is intended to be instrumental to this process. It establishes a framework for examining the connections, between the intrinsic characteristics of knowledge items, the capabilities that support and enable the creation of value and the achievement of the investigation goals. Building on theories and frameworks discussed in previous chapters, and in particular on the **CIHR Knowledge Translation model of health research knowledge into effective healthcare action** (CIHR, 2004; 2005), which integrates the research knowledge production and the application cycle, the following conceptual model for the implementation and management of the **Research Investigation life-cycle** is developed (Figure 22):
This process model aims to encourage a standard and comprehensive view over the entire lifecycle of the RI process, without being either too restrictive or too abstract and theoretical. The KDC Framework is not intended as a rigid structure, prescribing actions and steps to be followed in a strict order. Instead, the conceptual model is intended to be applied and interpreted flexibly, as it identifies the possible steps for the instantiation and optimisation of a RI process and the adoption and assimilation of innovations, including the pre- and post-conditions and their inter-dependencies. This allows the mapping and assessment of RI requirements against engineering and organisational characteristics (capabilities) of the context of implementation. The different elements of the model may occur in different orders in different circumstances, and/or be revisited a number of times forming iterative loops. The application of the Knowledge Discovery Cube Framework will allow establishing baseline references: general guidelines and benchmarks for the effective implementation of any RI process.

Following is a brief description of the Research Investigation life-cycle:

### 4.1 Design Phase

The design phase comprises activities, intended to investigate the requirements of a RI, assess its feasibility in the present context and, in case of barriers, produce appropriate recommendations to help overcome them. In the present work Research Investigations (RIs) are described as the design and implementation of dedicated studies targeting medicines safety issues or involving medicines safety data. They employ scientifically valid methods and relevant data evidence to achieve the defined objectives (i.e. create knowledge regarding the research questions to be
answered). The successful implementation of a RI is conditioned by the availability of required socio-technical capabilities, which represent critical organisational and operational enablers. An analysis of the investigation method, the data evidence employed and the capabilities supporting the investigation instance (required and available capabilities) is required. The activities taking place during the design phase can be summarised as follows:

- Definition of Research Questions;
- Identification of investigation method;
- Identification of data evidence to be employed;
- Current capability analysis.

**Current capability analysis** should examine the capability requirements of the intended RI (desired capabilities) against the existing capabilities (current capabilities) in the network (or in individual stakeholders), in order to identify **capability gaps** that are critical for the successful attainment of the goals and objectives of the RI. The process should review and accommodate the capabilities needs of all stages of the RI process (Data sourcing, Data processing, Analysis & reporting). **Capabilities management** could involve procurement/upgrading of existing capabilities (e.g. installation of a platform to process data centrally, adaptations in organisational structures etc). The process may also lead to new rounds of R&D research (**R&D planning**) in order to bring about the improvements in specific research areas needed to effectively implement the intended RI (e.g. development of more rigorous data mining methods). The latter is a case where the application of knowledge in practice triggers and influences subsequent rounds of research. The KDC Framework builds on the **ecosystem paradigm of collaborative knowledge creation**, approaching medicines safety investigations as a collaborative learning exercise: cross-disciplinary co-operations involving a diversity of partners who engage in mutual learning and jointly develop cooperative activities, combining their operational and organisational strengths to advance pharmacovigilance. Beyond the design and implementation of RIs, the KDC Framework is intended to facilitate partnership building for knowledge creation. In this context, an important dimension of the model is the identification of **Collaboration Impact Zones**. **Collaboration impact zones** are those junctures where interactions and the exchange of expertise and information are frequent, urgent, and complex: these may be focused on either internal or external collaboration. They help stakeholders focus on the right areas of collaboration to ensure that the benefits of collaboration are maximised. In the present context, collaboration impact
zones are focused on external (inter-organisational) operations, but can be further detailed to address internal (interdepartmental) operations that support a RI. The collaboration provisions (communication and collaboration tools, organisational aspects) need to be adapted to the specific requirements of each collaboration zone. Table 28 summarises capabilities management in the context of a RI.

Table 28. Capabilities management in the context of a RI.

| Map RI to Process steps | Map RI to Capabilities | Identify and describe process steps | Identify the capability requirements of the RI life-cycle. | Investigate capability requirements for each stage of the process. | Define desired (required) capabilities of the RI | Identify currently available capabilities of relevance to the RI. | Assess current/required strength/performance of capabilities | Derive demand strategies from capabilities gap: Define and prioritise Capabilities procurement and/or R&D actions |

The design phase should provide the necessary input for the effective implementation of a RI, allow for the investigation of critical factors and for the anticipation and mitigation of potential operational or organisational risks.

4.2 Implementation Phase

The implementation phase comprises the development of the investigation protocol, the collection of data evidence (harvesting data from selected databases or collecting data directly from data originators), data processing, analysis of outputs and reporting.

4.3 Evaluation Phase

The evaluation phase revolves around the systematic evaluation of both the outputs and the processes of the investigation. For this purpose appropriate methodologies are using, defining the criteria and performance indicators to be applied and outlining the actions to be taken.

4.4 Review Phase: Innovation & Improvement cycle

During the review stage a critical examination of the evaluation results is performed. The attained value of a RI is conditioned by the strength of the scientific method, the quality of the implementation, the availability of data evidence of value to the RI and the alignment of the
situational factors (capabilities). The identification of a performance gap, (i.e. that the RI instance failed to achieve its full potential) can trigger an optimisation cycle, to enhance, improve and better align the building blocks of the RI (method, data and capabilities).

The identification of an innovation gap, in the view of new innovations that have emerged, can trigger an innovation cycle for the adoption and assimilation of these innovations in the RI. The process is illustrated in the following figure (Figure 23):

![Figure 23. Innovation and Improvement cycle](image)

**Analysis of innovation points**

Adapting the methodology proposed by JRC/IPTS-ESTO (Braun, et al., 2003), for the analysis of innovation points a “footprint matrix” giving a snapshot of the situation as it pertains today (current mix of data, methods and capabilities) and an “emerging matrix” to display baseline innovation projections need to be developed. Based on these, the options deriving from the current (footprint-matrix) and emerging innovations can be analysed. Research Investigations can be illustrated in terms of the following dimensions: Data sourcing, Data processing, Analysis & Reporting. Within each of these, specific innovations have a range of potentially significant impacts (research translation). Reversely, these dimensions of RI can be seen as the major drivers that frame technology development in the field of pharmacovigilance (application to research, R&D planning). The matrix should display for each cell, spots representing the attainable value from the adoption of the respective innovations (Table 29).
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Table 29. Analysis of Innovation Impact

<table>
<thead>
<tr>
<th>Innovation</th>
<th>Sourcing</th>
<th>Data processing</th>
<th>Analysis &amp; reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innovation 1</td>
<td>Attainable value</td>
<td>Attainable value</td>
<td>Attainable value</td>
</tr>
<tr>
<td>Innovation 2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The options deriving from the current footprint-matrix and emerging matrix of innovative should be examined in the light of relevant influential situational factors, namely need to be examined in conjunction with the required capabilities. The resulting cube-shape analysis framework is illustrated in Figure 24. When examining the feasibility and value potential of a new innovation (being a new technology, a new scientific method etc) gap analysis can reveal the areas that will be well supported in terms of socio-technical capabilities. These are all key areas of opportunity to develop new studies (paths-in-potentia). The analysis could also reveal underserved areas, i.e. areas that may need watching for lack of socio-technical support. These are areas for organisational or operational action taking (e.g. through policy making).

![Figure 24. Analysis of innovation points](image-url)

Overall, the KDC Framework offers a global picture of the RI process as integrated within the research knowledge production and application cycle. Feasibility and effectiveness of the research investigation process stand at the centre of the framework, being viewed from a different angle throughout the RI life-cycle. An Optimisation and Innovation dimension is also included to close the cycle.
Table 30. Investigation Optimisation & Innovation analysis

<table>
<thead>
<tr>
<th>Design</th>
<th>Evaluation</th>
<th>Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>The design phase assesses the feasibility of a study and provides an estimation of its effectiveness.</td>
<td>Verify that the RI implementation is effective and adds value.</td>
<td>Critically examine the RI design and implementation in the light of the evaluation results, to identify potential Improvement/Innovation points.</td>
</tr>
<tr>
<td><strong>Dimensions:</strong></td>
<td><strong>Dimensions:</strong></td>
<td><strong>Dimensions:</strong></td>
</tr>
<tr>
<td>I: Is the RI doable? (Feasibility) Are the basic conditions for the implementation of the investigation being met? Are all the required sociotechnical capabilities available?</td>
<td>II: Is the output meaningful? (Attainable Benefit) Is the evidence produced meaningful for the targeted stakeholder group?</td>
<td>IV: can the RI be improved? (optimisation) What is the cause of the performance gaps identified? How can these be addressed?</td>
</tr>
<tr>
<td>II: Can it produce meaningful outputs? (Attainable Benefit) Is the evidence produced meaningful for the targeted stakeholder group?</td>
<td>III: Does the RI add value? Is it cost-effective? (Attained Benefit) Is the value/cost ratio in maintaining and performing the investigation improved (i.e. greater cost effectiveness)?</td>
<td>V: Can emerging innovations be assimilated to the RI? (Innovation) Do they offer value potential?</td>
</tr>
<tr>
<td>III: Can the RI add value? Is it cost-effective? (Attainable Benefit) Is the value/cost ratio in maintaining and performing the investigation improved (i.e. greater cost effectiveness)?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. Conclusion

Part B presented the developed Knowledge Discovery Cube Framework for collaborative, information-based innovation in the field of pharmacovigilance. The main components of this Reference Framework were discussed extensively, namely (a) its Constructs (concepts), representing the vocabulary of the domain, a “conceptualisation used to describe problems within the domain and to specify their interrelationships (Section 3), and (b) the model (Research Investigation life-cycle), i.e. a set of propositions or statements expressing relationships among constructs (Section 4). Particular emphasis was placed on establishing working links between research and practice to support continuous innovation and improvement. The KDC Framework delineates causal and explanatory relationships in “what is” and establishes practical references to facilitate the instantiation of investigations and the valorisation and assimilation of emerging domain knowledge and innovation for developing “what could be” (optimisation, innovation through translation of research into practice).
Part C: Evaluation of the KDC Framework

1. **Introduction: Verification and validation of the KDC Framework**

The validity of a research project is a measure of its accuracy and can be described in terms of internal and external provisions (Leedy & Ormrod, 2001). Internal validity examines whether sufficient controls are implemented during the study, in order to ensure that the conclusions drawn are truly warranted by the input data collected (verification). External validity confirms that the research outputs can be used to make generalisations about the world beyond the research context (validation). A rigorous and comprehensive approach is applied for the evaluation of the research work and the developed KDC Framework. For the purposes of **internal validation** a retrospective examination of the design process and research process is applied to verify that this model satisfies all design requirements. Results are outlined in the following section. External validation is intended to verify that the objective of the research work is accomplished with respect to the world beyond the research context. Therefore, for the purposes of **external validation** empirical confirmation is sought, through a rigorous and comprehensive approach that addresses three important dimensions: (a) validity and comprehensiveness, (b) applicability and usability and (c) added-value.

The process involves (a) an exploratory investigation of the KDC Framework’s ability to describe state-of-the-art drug safety cases taken from innovative research projects and (b) the operationalisation of the Reference Framework in the context of vaccine safety. The first method targets the first validation dimension (validity and comprehensiveness of the Reference Framework), while the second addresses all three dimensions. Operationalisation in the context of vaccine safety, intended as an **explanatory case study** that enables the validation of the developed concepts and structures using new empirical data. It should be stressed that validation in the context of vaccine safety is intended as a **formative instrument**, namely not solely to test a theory, but also to refine, improve, and extend it.

The evaluation process spanned several areas, including: a retrospective view of requirements; an investigation of the KDC Framework’s ability to describe state-of-the-art cases; and the application of the developed framework in the area of vaccine safety monitoring (ADVANCE project case study). The work of the ADVANCE project and particularly the development, implementation and evaluation of the first proof-of-concept study (ADVANCE POC 1) provided
valuable formative insight, revealing critical aspects and areas of potential improvement, thus contributing to the refinement of the Knowledge Discovery Cube Framework.

The validation the operationalisation of the KDC Framework in the context of the ADVANCE case study is discussed in Chapter 6.

2. Retrospective view of requirements

Three requirements verification loops are foreseen (Figure 13), in order to verify that the developed framework satisfies all design requirements. The high-level requirements and overall and refined objectives discussed in previous sections are summarised and revisited in the following tables.

Table 31. Review of high-level requirements

<table>
<thead>
<tr>
<th>High-level requirements</th>
<th>Verification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scope of the investigation</strong></td>
<td>The KDC Framework is purposely designed with a view on both the demand (practice) and the supply (research) side, aiming to accommodate investigations varying in scope, content, and maturity. The KDC Framework aims to serve as reference to build sustainable capacity for the proliferation of smart investigation spaces for drug safety questions.</td>
</tr>
<tr>
<td>Digitisation &amp; operationalisation, improvement &amp; optimisation, and discovery:</td>
<td></td>
</tr>
<tr>
<td>- From existing scientific processes to digital procedures: from as is to digital</td>
<td></td>
</tr>
<tr>
<td>- Exploring new paths</td>
<td></td>
</tr>
<tr>
<td>- Continuous innovation: discovery</td>
<td></td>
</tr>
<tr>
<td><strong>Instantiation of investigation</strong></td>
<td>The KDC Framework can serve the purposes of building sustainable capacity for drug safety investigations, promoting best practice and paving the way for successful and sustained innovation and improvement.</td>
</tr>
<tr>
<td>- Operational effectiveness</td>
<td></td>
</tr>
<tr>
<td>- Organisational alignment &amp; joint activity</td>
<td></td>
</tr>
<tr>
<td>- Quality</td>
<td></td>
</tr>
<tr>
<td>- Joint-up sources of knowledge: expanding evidence base</td>
<td></td>
</tr>
<tr>
<td>- Management of capacities &amp; continuous Improvement</td>
<td></td>
</tr>
</tbody>
</table>

Table 32. Review of high–level objectives

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Verification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective 1</td>
<td>The KDC Framework can be used to effectively assess the socio-technical ramifications of Research Investigations. All relevant analysis dimensions have been identified and described.</td>
</tr>
<tr>
<td>The implementation of the knowledge discovery process spans across the technical and the social continuum. The system needs to leverage technology and cutting-edge tools to advance the investigation, also balancing social and organisational aspects.</td>
<td></td>
</tr>
<tr>
<td><strong>Objective</strong></td>
<td><strong>Requirement</strong></td>
</tr>
<tr>
<td>--------------</td>
<td>----------------</td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>The knowledge discovery process combines tacit and explicit knowledge: data evidence and scientific judgment to produce insight (e.g. to infer causation). This creates the need for the availability of places of interaction, equipped with the appropriate tools for “knowledgeable stakeholders” to convene and deliberate.</td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>For the participating stakeholders, the knowledge discovery process is a continuous learning process. As technologies evolve and environmental circumstances change so must investigations learn from experience and adapt to the new circumstances: exploit the opportunities created in order to improve performance and mitigate potential risks.</td>
</tr>
<tr>
<td><strong>4</strong></td>
<td>Technology creates new capabilities for drug safety research moving towards data-intensive processes. The feasibility of such investigations in the digital pharmacovigilance ecosystem needs to be assessed and verified at the onset of a new investigation.</td>
</tr>
<tr>
<td><strong>5</strong></td>
<td>During an investigation, resources internal and external to the participating organisations are mobilised, creating technical and organisational interdependence among stakeholders.</td>
</tr>
<tr>
<td><strong>6</strong></td>
<td>Stakeholders should be able to handle innovations and changes in core components of an investigation in an effective and timely manner.</td>
</tr>
<tr>
<td><strong>7</strong></td>
<td>Stakeholders should be able to recognise emerging innovations and changes that could affect investigations.</td>
</tr>
</tbody>
</table>
Chapter 4: The Reference Framework

Objective 8: Stakeholders should seek new knowledge, explore new directions to improve the quality and expand the scope of medicines safety.

Key to the KDC approach is adaptability of its orientation and capacity development services, so that they remain relevant to evolving requirements. To this end, the KDC Framework proposes a dynamic environment for RI, supporting an ongoing dialogue within the stakeholder community and the continuous study of the medicines safety evidence base, so as to ensure its timely updating to facilitate and support effective service provision and coordination.

Objective 9: Stakeholders should be able to assess the success of the implemented investigations.

Evaluation of outcomes and processes represents an important component of the KDC Framework model. Combined with the in-depth investigation of capabilities insight and recommendations can be produced to use the evaluation results to further improve the RI process.

Table 33. Review of low–level requirements

<table>
<thead>
<tr>
<th>No</th>
<th>Refined (Low level) requirements</th>
<th>Verification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>enable the simultaneous optimisation of both technical and social elements in the design of pharmacovigilance innovations</td>
<td>Holistic examination and management of capabilities (technologies-, people-, and organisation-related factors).</td>
</tr>
<tr>
<td>2</td>
<td>enable the balancing of interdependent components (people, goals/tasks, structure and technology)</td>
<td>Capabilities are viewed holistically and in conjunction with the data and methods employed and the objective to be achieved</td>
</tr>
<tr>
<td>3</td>
<td>analysis of pharmacovigilance innovation as an open system</td>
<td>The KDC Framework builds on the ecosystem paradigm of collaborative knowledge creation. The pharmacovigilance system as a whole and stakeholder organisations individually, are viewed as open systems interacting with their environment (continual evolution)</td>
</tr>
<tr>
<td>4</td>
<td>enable the analysis of planned and unplanned changes in the involved work systems, associated with pharmacovigilance innovation</td>
<td>Formal projects and unplanned changes (ongoing adaptations and experimentation) are accommodated by the Research Investigation life-cycle</td>
</tr>
<tr>
<td>5</td>
<td>allow for continuous and in situ analysis of the PV innovation instantiation</td>
<td>The review phase of the Research Investigation life-cycle allows for continual improvement and innovation</td>
</tr>
<tr>
<td>6</td>
<td>ensure relevance of outcomes to stakeholder groups</td>
<td>Collaborative learning exercise: cross-disciplinary co-operations involving a diversity of partners who engage in mutual learning and jointly develop cooperative activities, combining their operational and organisational strengths</td>
</tr>
</tbody>
</table>
### Chapter 4: The Reference Framework

<table>
<thead>
<tr>
<th>No</th>
<th>Refined (Low level) requirements</th>
<th>Verification</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>enable the joint analysis of social and technical parts</td>
<td>social and technical parts are treated as inseparable. Any actor, whether person, object (including computer software, hardware, and technical standards), or organisation, is equally important</td>
</tr>
<tr>
<td>8</td>
<td>allow for the identification andaccommodation of the needs of individual stakeholders and groups</td>
<td>collaboration impact zones catering for external (inter-organisational) operations, and internal (interdepartmental) operations that support a RI</td>
</tr>
<tr>
<td>9</td>
<td>allow for synthesis andconsolidation of individual group perspectives</td>
<td>Collaborative learning exercise among participating stakeholders aimed at the consolidation of perspective towards a common benefit</td>
</tr>
<tr>
<td>10</td>
<td>enable the analysis of theinnovation’s relevance to the technological, organisational and environmental context</td>
<td>Capabilities assessment is performed during the design phase and can point to new R&amp;D</td>
</tr>
<tr>
<td>11</td>
<td>enable the analysis of theinnovation’s fitment and viability</td>
<td>The evaluation phase involves the systematic evaluation of both the outputs and the processes of the investigation. During the review stage a critical examination of the evaluation results is performed to initiate a cycle of Innovation or Improvement.</td>
</tr>
<tr>
<td>12</td>
<td>enable the analysis of the effects of innovation on both a macro- and a micro-level.</td>
<td>The KDC Framework can accommodate analysis of RI at a system (Macro-) and at an organisation/department level (micro-level)</td>
</tr>
<tr>
<td>13</td>
<td>enable the analysis of the effects of organisational culture</td>
<td>Organisational culture forms part of the capabilities considered for and during a pharmacovigilance investigation</td>
</tr>
<tr>
<td>14</td>
<td>ensure relevance of governance and organisation structures to the implementation environment</td>
<td>design of an organisation and its subsystems (Structure and management) must ‘fit’ with the environment.</td>
</tr>
<tr>
<td>15</td>
<td>allow for continuous discourse and exchange among stakeholders</td>
<td>Organisational knowledge is created through a continuous dialogue between tacit and explicit knowledge</td>
</tr>
<tr>
<td>16</td>
<td>enable the harnessing of organisational knowledge</td>
<td>A RI is essentially a Knowledge Management exercise that builds on knowledge contained in both information sources and people. Capabilities therefore need to be examined from both perspectives, as they entail both an information management and a behavioural aspect. The first perspective builds on the notion of knowledge as an object that can be captured and transferred. The second views KM as a collaborative knowledge creation process that is unique to each individual.</td>
</tr>
<tr>
<td>17</td>
<td>allow for continuous assessment of effectiveness and the identification performance gap</td>
<td>Review Phase: Innovation &amp; Improvement cycle</td>
</tr>
<tr>
<td>18</td>
<td>allow for the identification and removal of barriers</td>
<td>Capabilities management (on a macro- and micro-level). Participating organisations should be able to balance their capabilities against the requirements stipulated by their role in the RI</td>
</tr>
<tr>
<td>19</td>
<td>allow to determine the decidability and effective calculability of a proposed investigation</td>
<td>Scientifically valid methods are examined in conjunction with the availability of relevant data evidence and required socio-technical capabilities, which</td>
</tr>
</tbody>
</table>
## Chapter 4: The Reference Framework

<table>
<thead>
<tr>
<th>No</th>
<th>Refined (Low level) requirements</th>
<th>Verification</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>allow to determine the virtualisation of a proposed investigation</td>
<td>Feasibility analysis of the investigation method, the data evidence employed and the capabilities supporting the investigation instance (required and available capabilities)</td>
</tr>
<tr>
<td>21</td>
<td>allow to determine the computational complexity of a proposed investigation</td>
<td>Current capability analysis examines the capability requirements of the intended RI (desired capabilities) against the existing capabilities (current capabilities) in the network (or in individual stakeholders), in order to identify capability gaps that are critical for the successful attainment of the goals and objectives of the RI.</td>
</tr>
<tr>
<td>22</td>
<td>enable systemic capacity building</td>
<td>Capabilities management could involve procurement/upgrading of existing capabilities in terms of (1) structures, systems and roles, (2) staff and facilities, (3) skills, and (4) tools.</td>
</tr>
<tr>
<td>23</td>
<td>enable the formation of structured collaborations among pharmacovigilance stakeholder organisations to accommodate knowledge exchange processes</td>
<td>Beyond the design and implementation of RIs, the KDC Framework is intended to facilitate partnership building for knowledge creation. In this context, an important dimension of the model is the identification of Collaboration Impact Zones.</td>
</tr>
<tr>
<td>24</td>
<td>enable disruptive innovation practices</td>
<td>Review phase: the principal innovation trigger in medicines safety investigations are advances in technology, which generate and allow access to new sources of evidence and improve data processing and insight generation processes. This is not a one-way process moving from technology innovation to drug safety innovations, but a reciprocal process of interaction and exchange, with requirements collected and lessons learned during the instantiation leading to process improvements or influencing subsequent rounds of research.</td>
</tr>
<tr>
<td>25</td>
<td>enable absorptive capacity building in pharmacovigilance stakeholder organisations to accommodate knowledge exchange processes</td>
<td>The KDC Framework, is intended as an instrument to increase the absorptive capacity of partners organisations to better accommodate the knowledge exchange processes that form part of the pharmacovigilance investigation</td>
</tr>
<tr>
<td>26</td>
<td>enable the alignment of the information processing capability of pharmacovigilance stakeholder organisations with the information processing needs resulting from their involvement in pharmacovigilance innovations</td>
<td>Fitment between an organisation’s information processing needs stemming from the organisation’s involvement in a RI and their information processing capability is a determinant of performance of the RI process and represents a key objective of the KDC Framework</td>
</tr>
<tr>
<td>27</td>
<td>enable dynamic capability building</td>
<td>The KDC Framework is dynamic. It establishes practical references to facilitate the incorporation of emerging domain knowledge and technological innovation, including dynamic capability building in organisations to effectively adapt their resource base to emerging needs of RIs.</td>
</tr>
<tr>
<td>No</td>
<td>Refined (Low level) requirements</td>
<td>Verification</td>
</tr>
<tr>
<td>----</td>
<td>---------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>28</td>
<td>enable the multi-level assessment of the value proposition of pharmacovigilance innovations</td>
<td>Different analysis perspectives can be accommodated in order to make the insights generated actionable.</td>
</tr>
<tr>
<td>29</td>
<td>enable forward thinking and strategic planning to anticipate and accommodate pharmacovigilance innovations</td>
<td>Forward thinking and the accommodation of innovation triggers (particularly technology triggers) form an integral part of the KDC Framework. The KDC Framework considers RIs as being constantly in a state of “imperfect development”, with evaluation and foresight shaping the ground for continual improvement and innovation.</td>
</tr>
<tr>
<td>30</td>
<td>enable collective creative design for pharmacovigilance innovation</td>
<td>The KDC Framework accommodates the different aspects of collaborative creativity, allowing to: (i) explore the whole conceptual potential of the initial concept, (ii) involve and support people in a rule-breaking process, (iii) enable relevant knowledge activation, acquisition and production, and (iv) manage collective acceptance and legitimacy of rules (re)building.</td>
</tr>
<tr>
<td>31</td>
<td>enable the analysis of the performance of pharmacovigilance innovation systems and processes</td>
<td>The evaluation phase revolves around the systematic evaluation of both the outputs and the processes of the investigation.</td>
</tr>
</tbody>
</table>

### 3. Discussion

As part of the evaluation of the KDC Framework a retrospective examination of the multi-level requirements identified in Part A of the present Chapter was performed. Overall, the KDC Framework is aligned with requirements set, possessing the required comprehensiveness and flexibility to accommodate the complexity of its intended application setting. The practical applicability and relevance of the Framework is the subject of the empirical validation in the context of the ADVANCE project. The validation work and the conclusions draw are discussed in Chapter 5.
Chapter 5: The ADVANCE case study

Introduction
The ADVANCE project provided the backdrop for the empirical validation of the KDC Framework. The present research developed a symbiotic bidirectional relationship with the project, following, complementing and supporting the work of ADVANCE (contributing to the creation of the POC study evaluation framework, the evaluation of the first POC study and assisting the planning and organisation of the subsequent POC investigation) and learning and being informed by the work and outcomes of the project. Feedback regarding the progress and challenges of the project was both formative to the development of the KDC Framework and evaluative. In line with the Nonaka-Takeuchi theory of knowledge creation (Nonaka & Takeuchi, 1995), the KDC Framework validation was a spiraling learning process, rooted in actions and experiences taking place within an expanding “community of interaction”, as well as in formal feedback related to the operationalisation of the Framework. Validation involved both formal and informal steps, tacit and explicit knowledge creation. Informal steps included participant observation, document analysis, project meetings, presentations and discussions about the scope, progress and activities of the project. Formal steps included working meetings and workshops, revolving around instruments and processes developed to support POC study instantiation and management (generic reference model) and evaluation (evaluation framework) on the basis of the KDC Framework. The operationalisation of the KDC Framework in ADVANCE was twofold. Two instruments were developed on the basis of the KDC Framework: the ADVANCE generic reference model and the ADVANCE POC study Evaluation Framework, each drawing from a different area of the KDC Framework (Figure 25).

The present Chapter is structured as follows: Firstly, the ADVANCE case study and the lessons learned are discussed in Part A. Parts B & C refer to the operationalisation of the Framework, outlining the work performed on the basis of the KDC Framework for the evaluation of POC studies (Part B) and for the development of instruments and processes to support POC study instantiation and management (Part C) and describe the process and findings of the KDC evaluation in the context of ADVANCE (formative and summative instruments). Qualitative
feedback was collected at various points of the project work. In Parts B & C significant instances of explicit feedback collection are outlined.

Figure 25. Operationalisation of the KDC Framework in ADVANCE
Part A: The ADVANCE case study

1. About the ADVANCE Case study

Case studies provide detailed contextual analysis of a limited number of events and their relationships. Typically case study data is used to complement the knowledge gained from the world of theory, to verify and validate that the research outcome meets the design requirements, correlates with existing knowledge from the world of science and contributes new knowledge to this field. In the present inquiry, case study analysis is an instrument utilised to verify and validate that the developed Research Framework correlates with pragmatic needs and provides added-value to the field. The present case study focuses on vaccine benefit/risk assessment studies, which form an integral part of vaccine pharmacovigilance. Site of the case study is the ADVANCE research project, which focuses on the development and testing of methods and guidelines for the rapid delivery of reliable data on the benefits and risks of vaccines that are on the market. In addition to the theoretical study of the case, in the context of the ADVANCE project operationalisation and real-life validation of the KDC Framework is pursued.

A major barrier to the empirical validation of holistic frameworks and forward looking methods is that it is very difficult to get new theoretical approaches accepted and used in practice. The ADVANCE project, being a research initiative itself, but grounded in real-life practice and representing all the key stakeholders in the field, provided a valuable backdrop for the empirical validation of the KDC Framework. The choice of ADVANCE as case study site represents both an illustrative example and a critical instance of the KDC framework. In its illustrative sense the ADVANCE case study is intended to provide realism, vividness, and in-depth information about the practical implementation of the Framework. As a critical instance, the case study serves both the purposes of exploration and evaluation, i.e. functions as a source of insight and a critical test of the framework’s applicability, questioning the highly generalised assertions it contains and whether these are valid through examining one instance. While the ADVANCE project focuses on a specific subdomain of pharmacovigilance and has a limited scope in terms of the evidence sources considered, the project has a broad scope with regards to use cases (vaccine safety and benefit-risk studies), which is aligned to the present research. The work of ADVANCE lends itself to the scope of the practical investigation and validation of the KDC Reference Framework. The ADVANCE case, has allowed examining the validity of the KDC
Chapter 5: The ADVANCE case study

Framework in two dimensions: (a) **Operational**: as a guide in the developmental purpose of Research Investigations (vaccine benefit/risk assessment studies) **fit, relevance, workability, and modifiability** (exploratory analysis); and (b) **Conceptual**: examining the **accuracy and completeness of concepts and constructions** (confirmatory analysis).

Engagement with the ADVANCE project has been **prolonged** and not limited to the evaluation of the KDC Framework (Figure 26). Extended exchange was deemed important for ensuring the **interpretive validity** (Maxwell, 1992) of the present research in the **thick description** purpose sense (Geertz, 1973), as **prolonged immersion and engagement allow to interpret locally constructed meanings from an insider’s perspective** (Donmoyer, 2001). The present research developed a symbiotic bidirectional relationship with the ADVANCE project, following, complementing and supporting the work the project (contributing to the creation of the POC study evaluation framework, the evaluation of the first POC study and assisting the planning and organisation of the subsequent POC investigation) and learning and being informed by the work and outcomes of the project. From a theoretical point of view this phase of the research work involves extensive **participant observation**, which could be described as a case of **action research** (Baskerville, 1999), as it is focused at solving current practical problems while expanding scientific knowledge.

**Figure 26. Exchanges between ADVANCE and the KDC research study**

While in ADVANCE emphasis has been placed on the scientific aspects of protocol development, on overall governance and compliance issues, and on information layer interoperability, data aggregation and processing, the project has been **lacking a life-cycle**
Chapter 5: The ADVANCE case study

perspective on vaccine safety and benefit-risk studies and a holistic methodology to systematically approach this life-cycle. The present research work can help address this shortcoming, which became particularly evident during the evaluation of POC1 study. Among the lessons learned from the evaluation of POC1 was the need for systematisation and transparency.

Furthermore, being involved in the assessment of the feasibility and effectiveness of the POC cases, issues related to knowledge translation became evident during POC1 that fell into the scope of the KDC Framework. Practical approaches and solutions building on the KDC Framework were proposed and adopted by the project for POC study evaluation and for scaling and generalising vaccine benefit/risk assessment studies. The KDC Framework informed the development of the POC evaluation strategy, and was used as a reference to develop a generic framework and tools to guide the implementation of the evidence creation process for any vaccine benefit/risk research question in the future (i.e. how to define, implement, sustain and improve an investigation/research protocol, based on the ADVANCE architecture). As illustrated in Figure 26, ADVANCE provided the present research work with valuable insight and formative feedback in the course of the first proof-of-concept study (POC1) and the extensive consultations for the interpretation of the evaluation results of POC1. The process included:

- **Document analysis**, including the review of all relevant work documents and internal communications, and of reports, deliverables and other formal outputs of the project;
- **Participant observation**, as part of the activities of the project;
- **Work meetings and workshops**, mainly revolving around the organisation and structuring of the evaluation work;
- **Focus group discussions**, with selected experts.

The operationalisation of the KDC Framework, which coincided with the planning of the second POC study (POC2), was adapted to the specific requirements of vaccine b/r studies, to facilitate the planning and organisation of POC2. **Working meetings** with experts from the ADVANCE project (members of the project’s Steering Committee) were organised to discuss the implementation and management of vaccine b/r studies using a structured methodology. A **dedicated expert focus group meeting** was organised to validate the KDC Framework and its operationalisation instruments. Analysis was qualitative and participative/opinion, with discussions revolving around the topics of (a) validity and comprehensiveness, (b) applicability
and usability and (c) added-value. Detailed information about the ADVANCE project and the quality of its workplan and partnership is provided in Appendix 2. Appendix 1 features background information on vaccine pharmacovigilance. The following section discusses lessons learned from immersion in and the study of the ADVANCE case. The operationalisation and validation of the KDC Reference Framework in the context of vaccine safety monitoring are presented and discussed in detail in Parts B and C.

2. Learnings from the study of the ADVANCE case

As part of the case study, comprehensive and in depth information was collected about the ADVANCE project, about benefit-risk study design and implementation, and about the first proof-of-concept study implemented (POC1). The purpose of this activity was confirmatory (Flyvbjerg, 2006). To this end, multiple sources of evidence were used, for comprehensive depth and breadth of inquiry (observation, document analysis etc.). This section summarises specific conclusions of interest to the present research that were drawn from the study of the ADVANCE case, with regards to the organisation of vaccine studies, including relevant lessons learned from POC1. The challenges experienced and other limitations identified motivated the researcher to develop the Generic ADVANCE process map, building on the principles of the KDC Framework. The instantiation of the KDC Framework is discussed in detail in the following parts. Particular attention was placed to the work of the expert Review Panel set up in WP7 (Implementability analysis) to review deliverable D5.1 (Report on available information technology platform and processes for proof-of-concept studies), which sets the foundations for the implementation of POC studies. The WP5 Review Panel (RP5) defined evaluation criteria for each element of the D5.1, which in the present context represent requirements that should also be supported by the KDC framework instruments.

2.1 Characteristics of ADVANCE benefit-risk studies

ADVANCE is aimed at the rapid evaluation, ad-hoc assessment and continuous monitoring of the impact of vaccination, by harnessing real-time data from large observational databases. Work revolves around the development of an infrastructure for integrated studies of post-approval benefit/risk assessment. Nonetheless, challenges go beyond technical feasibility, to also include questions of governance and coordination, heterogeneity in the scientific and organisational focus and interest of the involved entities etc. The ADVANCE benefit-risk studies leverage
existing electronic healthcare data from multiple sources for the generation of actionable knowledge within an interconnected network of public and private organisations, in which people from different disciplines collaborate, and should abide by regulatory and ethical rules. To facilitate the implementation of vaccine benefit-risk studies, ADVANCE builds has built an evidence generation environment in which this could be possible, using specific tools and workflows to plan, manage and implement the evidence generation pathway, with the help of best practice guidance, and following the designated Code Of Conduct for research procedures. Four pillars can be identified: (a) **Protocol**: Study aim scoping, Protocol development and Study team forming; (b) **Data access**: Data access, approvals, data transfer and acquisition (including process and tools); (c) **Analysis**: Performing the analyses (IT tools, skillset, quality, specifications and documentation) and reporting (tools, format of outputs/reports); and (d) **Decision making**: Insight generation and decision making, Scientific quality and impact of outputs (scientific value, relevance for B/R decision making). The ADVANCE benefit-risk studies can be decomposed and described as follows: vaccine benefit-risk study is a **process** that builds on **knowledge**, is **collaborative**, and occurs within a given **context**, and is aimed at generating **outputs**. The ADVANCE mission highlights the following aspects: **timeliness** (to be increased), **collaboration** (to be fostered and facilitated), and **quality** and **acceptance** of outputs (to be improved). Based on the analysis of the ADVANCE case, the defining attributes of benefit-risk studies can be summarised as follows:

**Table 34: definitive attributes of benefit-risk studies**

<table>
<thead>
<tr>
<th>Item</th>
<th>Defining attributes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process</td>
<td>Complexity</td>
</tr>
<tr>
<td></td>
<td>Quality</td>
</tr>
<tr>
<td></td>
<td>Transparency (fairness, independence, protection, integrity, and communication)</td>
</tr>
<tr>
<td></td>
<td>Acceptability</td>
</tr>
<tr>
<td></td>
<td>Speed and time-efficiency</td>
</tr>
<tr>
<td></td>
<td>Cost-efficiency</td>
</tr>
<tr>
<td></td>
<td>Feasibility</td>
</tr>
<tr>
<td></td>
<td>Relevance</td>
</tr>
<tr>
<td></td>
<td>Effectiveness/value</td>
</tr>
<tr>
<td></td>
<td>Application-oriented</td>
</tr>
<tr>
<td></td>
<td>Micro- and macro-level (individual, organisational, regulatory perspective)</td>
</tr>
<tr>
<td></td>
<td>context-driven</td>
</tr>
<tr>
<td></td>
<td>Usability of methods and instruments</td>
</tr>
<tr>
<td></td>
<td>Applicability and acceptability of methods and instruments</td>
</tr>
<tr>
<td></td>
<td>Generalisability and Transferability</td>
</tr>
<tr>
<td></td>
<td>Scaling</td>
</tr>
<tr>
<td></td>
<td>Comprehensiveness</td>
</tr>
<tr>
<td></td>
<td>Efficiency</td>
</tr>
<tr>
<td>Item</td>
<td>Defining attributes</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Knowledge | Feasibility of data access  
|          | Data processing and analysis  
|          | Insight generation and decision making  
|          | Ethical considerations  
|          | Approvals & authorisations  
|          | Privacy, confidentiality/Anonymity and security                                   |
| Collaboration | Collaboration and Transparency  
|          | Fairness, independence, protection, and integrity  
|          | Equity  
|          | Formation of competent scientific teams  
|          | Public-private collaborations  
|          | Generic, flexible governance model  
|          | Trust building  
|          | Conflicts of Interest  
|          | Code of Conduct                                                                 |
| Context | Compliance with regulations, legislation, standards and approvals  
|          | Compliance with institution/organisation practices and policies  
|          | Scientific independence and public trust  |
| Outcomes | Meaningful and useful outputs  
|          | Applicability: actionable, practical outputs for insight generation and decision making  
|          | Timeliness and speed  
|          | Scientific quality of outputs  
|          | Public health interest  
|          | Impact of outputs  
|          | Relevance for B/R decision making  
|          | Acceptance by stakeholder groups (Stakeholder satisfaction)  
|          | Accuracy, Validity and Credibility  
|          | Innovation  
|          | Added value                                                                   |

The present analysis highlights the need for establishing detailed processes and workflows, and for better alignment of capabilities and resources, improved collaboration, transparency, and more rigorous management over the study process. The study implementation should be systematic and organised, multidimensional, participatory, context-driven, and application-oriented, in order to yield outcomes that are relevant, meaningful and useful, scientifically robust, timely and applicable. Effective and transparent collaboration among team members is deemed imperative. At any given stage of the study process, domain experts should be engaged, with the establishment of interactive and dialogue-based “spaces” for multidisciplinary collaboration and exchange of knowledge. Overall, transparency is deemed important for building trust both within teams of people with shared responsibilities and challenges (PI teams, statisticians, data custodians) and globally. The study process is intended to facilitate the exchange of knowledge and development of shared understanding among researchers,
practitioners and policymakers, at both individual and organisational levels. While acknowledging the contribution and expertise from participating organisations and the benefits of the resulting synergy, it is important to be transparent about potential conflicts of interest. A set of good practice principles (Code of Conduct) is proposed to guide vaccine study collaborations, including the definition of roles and responsibilities. The ADVANCE Code of Conduct includes 45 recommendations for 10 topics: scientific integrity; scientific independence; transparency; conflicts of interest; study protocol; study report; publication; subject privacy; sharing of study data; research contract. The development of the POC1 study was a long and reflective process, involving interaction with the implementation context and participants. Challenges the project had to overcome include the lack of rapid access to available data sources and expertise; the fragmentation of data, stored in geographically limited and non-standardised databases; restrictions of access and delays in obtaining the required legal/ethical authorisations; the need for managing potential conflicts of interest; difficulties inherent in establishing efficient interactions between multiple stakeholders, the complex interactions needed to comply with the internal procedures of the various stakeholders, etc. The analysis revealed two important antecedents to the process of implementing vaccine benefit-risk studies that relate to explicit and implicit sources of knowledge, namely, to the availability of relevant data sources of sufficient quality, and of expertise (professional knowledge). ADVANCE harnesses data from health vaccination data from multiple sources, and ensures high scientific quality, by engaging multiple experts and creates added value through wide collaboration, in contrast to studies by individual organisations, where useful expertise may be missing. This highlights the need to develop effective mechanisms for assessing and harnessing data sources and expertise and for supporting the formation of study teams and the alignment of work among the team members. Data relevant to vaccine studies spread over different types of organisation (disease surveillance networks, public health institutes, vaccine registries, vaccine manufacturers, academia etc.), are stored in heterogeneous databases of varying quality. Other important aspects of data sharing include questions of data protection, data ownership etc. Readiness to implement vaccine studies involves preparedness of data sources (database characterisation, harmonised coding schemes, data extraction modules, authorisations of use etc.), preparedness of Human Resources (availability of experts, clearance of conflicts of interest etc.) and availability of infrastructure and tools for data analysis and insight generation. It further implies the existence of a Code of
Conduct and governance models to guide the planning, creation and structure of a collaboration or partnership for monitoring the benefits-risks of vaccines. The actual study design results from thoughtful planning that revolves around the contextualisation of scientifically robust study protocols and methods within a given study implementation setting. Building on the affordances of new information and communication technologies, new vaccine study methods can be developed for the comprehensive investigation of vaccine benefits and risks. Translating into practice and instantiating these methods calls for effective and context-aware systematisation. The ADVANCE Framework for structured B/R analysis, developed a set of principles, guidelines and tools to guide decision-makers in selecting, organising, understanding and summarising evidence relevant to benefit-risk decisions. The analysis revealed that success in implementing vaccine studies depends on timely access to appropriate data, experts and infrastructures, on the use of scientific methods of analysis and the existence of a well-structured and principled framework for collaboration, and ensuring transparency. Timeliness is closely linked to preparedness for commencing vaccine studies, namely, to prior capacity building by prearranging necessary elements (centrally and at organisational level) and requirements. Project work also revealed the need for more insight into the study instantiation process. The design and implementation of POC1 followed the typical directions and principles of research-to-action Knowledge Translation (Glasgow et al., 1999; Straus et al., 2009; Straus et al., 2013; Harvey & Kitson, 2015), highlighting and successfully addressing challenges inherent to bringing research to action, and issues that relate to the instantiation life-cycle. From revisiting the strategic objectives of the project (Appendix 2), which emphasise timeliness and rapid responsiveness to decision making needs (“accelerated assessment”, “continuous monitoring”, “best evidence at the right time”), it can be concluded that steps towards generalisation are needed, in order to ensure ADVANCE’s ability to rapidly setup and implement study designs, and to decrease the time needed to access and evaluate information. By comparing the case against the features of the KDC Framework, the potential for further systematisation of the study process emerges, in the direction of increasing its operationalisation potential, supporting sustainance, facilitating maturity improvements and benchmarking, and enabling continuous innovation.
Part B: Operationalisation of the KDC Framework for POC study Evaluation

1. ADVANCE POC study Evaluation Framework

The principles outlined in the KDC Framework were used to inform and shape the POC evaluation strategy (POC Evaluation framework), as detailed in Abbasi et al. (2016). The POC Evaluation framework is aimed at providing appropriate methodology and systematic guidance, for the evaluation of the ADVANCE outputs. POC studies are conducted within the ADVANCE project in order to evaluate and provide evidence of the usability and effectiveness of proposed guidance and methods of integration and collaboration and on the added value of the project’s outcomes (time, cost, quality etc). The POC evaluation is therefore intended to provide a backdrop for systematic assessment of whether the ADVANCE approach and concepts are acceptable and good enough to be recommended for “release into production” in the final ADVANCE blueprint. In this light, the development of the evaluation method, rather than being approached as a static measure of the success (feasibility and effectiveness) of a single POC study, it is also intended to investigate upcoming POC investigations and ultimately support the generalisation of the ADVANCE Framework. Building on the KDC Framework, the implementation of a POC study was approached as a collaborative knowledge discovery process, in which distinct components interplay (“Data”, “Tasks”, “Actors”, “Technology”, “Organisation”). The structure and organisation of the ADVANCE project entails and implies a similar classification, while focusing on the most prominent, high-level dimensions (data sources and methods). In a given context, safety monitoring mechanisms make use of the available information sources and relevant socio-technical capabilities to achieve value. An in-depth investigation of the socio-technical ramifications of knowledge discovery is imperative in order to develop effective work methods for knowledge extraction in real-life situations. The feasibility and effectiveness of the POC investigation process on the basis of the critical questions included in Table 23 stand at the core of the analysis work. The POC investigation leverages the available knowledge sources, technologies and cutting-edge tools to advance the investigation, while balancing the environmental/organisational dimensions. The first aim should
be to assess the attained benefit (realised value) and interpret how this was achieved, i.e. the realised value and the contributing factors Figure 27).

POC1 pilot

Figure 27. Realised value and the contributing factors

The following five areas of value were defined for the evaluation of POC studies:

- Area 1: Process workflow and IT infrastructure/platform;
- Area 2: Scientific validity and innovation;
- Area 3: Quality (quality of data sources, standards, and regulatory compliance and legal);
- Area 4: Stakeholder satisfaction, and collaboration (Code of conduct, rules of governance, mutuality, administration, partnership, communication and engagement);
- Area 5: Privacy and Ethics (Privacy, Ethics, Integrity, Trust, Safety, and Confidentiality & Security).

For each of these areas relevant analysis dimensions and parameters have been considered (for example: Time, cost, quality, effectiveness, transparency, availability etc), on the basis of which relevant indicators and questions were defined (Table 35). Evaluation is focused on both the outcomes (vertical dimension).and the work processes (horizontal dimension) of a POC study. Evaluation work defines quality and performance criteria and indicators that permeate the entire study process. In order to be able to extract meaning from the results of the evaluation and facilitate action, performance indicators were mapped on the phases of the POC study process. Overall, performance indicators referring to the planning stage can be used to assess the feasibility of the study, i.e. to examine whether or not the preconditions for the execution of a
scientifically and operationally valuable study, and one that complies with legislation, standards, relevant codes of conduct etc. and governance rules are met.

Table 35. Mapping of KPIs on the phases of the POC study process

<table>
<thead>
<tr>
<th>Indicator ID</th>
<th>Evaluation area</th>
<th>Dimension (What?)</th>
<th>Indicator (What?)</th>
<th>Scoping</th>
<th>protocol writing</th>
<th>Data transformation</th>
<th>Analysis</th>
<th>Reporting</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>Process</td>
<td>Acceptability</td>
<td>Acceptability of study proposal, workflow, and overall implementation of the process - report by stakeholders</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>☑</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Definition of research question and choice of benefit/Risk scenario</td>
<td>✗</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Choice of study research teams, investigators</td>
<td>✗</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Protocol development</td>
<td>✗</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Protocol review</td>
<td>✗</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Protocol approval</td>
<td>✗</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Data source selection</td>
<td>✗</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Data source approval</td>
<td>✗</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Data storage</td>
<td>✗</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Data protection, privacy and security</td>
<td>✗</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Code of Conduct</td>
<td>✗</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Indicators referring to the study sourcing and the execution phase (i.e. the two implementation stages) can be used to verify compliance (i.e. verify that the study execution complies with the rules and conditions set during the planning stage and described in the study protocol) and assess the quality of the implementation (e.g. examine the quality of the tools and infrastructure employed in the study, measure run times etc.) Overall (high level) Indicators can be used to assess end-to-end performance and outcomes, including delays in the transition between process steps. To improve the quality of POC studies, and to make evaluation work actionable, this information is included in the Process Planning Canvas, through which it can be directly linked to the data inputs, activities and capabilities employed. While the primary scope is to prove the feasibility of the POC1 investigation design and to verify that it has the potential of being used for generating evidence on potential risks of medicines, analysis should not be limited to this. In a constantly evolving scientific and technologic environment, all three degrees of value described in Chapter 4 (B3.2) should be considered: realised (actual value achieved by the POC study as implemented), probable (optimal value achievable through the application of the most rigorous consolidated methods), potential (value proposition of emerging innovations). Potential performance or innovation gaps can subsequently be estimated (as discussed in Chapter 4 (B4.4) to take corrective measures or initiate an innovation cycle. Consequently, the evaluation process involves the following four stages:
Capítulo 5: El estudio de caso ADVANCE

► Estadio 1: Análisis descriptivo para la toma de conciencia

Para este propósito se realiza un análisis cuantitativo del caso POC1, con el objetivo de interpretar los resultados de la encuesta (resultados cuantitativos), teniendo en cuenta los aspectos Process, Code of conduct, Quality, Stakeholder satisfaction, Scientific validity and IT infrastructure, y para identificar las fortalezas reales y debilidades de la implementación actual de POC1. Este proceso analizará el valor real y el mapa “what?” a “how?”.

► Estadio 2: Análisis prescriptivo (fijando estándares para la optimización de POC1)

El benchmarking es el proceso de comparar los procesos de negocio y métricas de rendimiento de una empresa con las prácticas industriales mejoradas. Las dimensiones típicamente medidas son calidad, tiempo y costo. El benchmarking se enfoca en identificar, estudiar, analizar y adaptar las mejores prácticas y aplicar los resultados. En el contexto de la evaluación de POC1, el objetivo es identificar el beneficio óptimo (valor probable) que se puede obtener a través del uso de los métodos consolidados en el presente. Las preguntas a las que se deben responder son: ¿Cuánto podemos mejorar en la investigación de POC1? ¿Qué son los requisitos y precondiciones?

► Estadio 3 Análisis recomendativo (potencial de innovación)

Este estadio se refiere a la perspectiva futura. El objetivo es investigar la proposición de valor de las innovaciones emergentes para evaluar el beneficio potencial que se puede obtener a través de la consolidación y mainstreaming de las innovaciones emergentes en los ámbitos socio-technológicos relevantes. Las preguntas a las que se deben responder son: Existe oportunidad para mejorar aún más? En cuáles áreas socio-technológicas (por ejemplo, nuevas tecnologías, métodos)? ¿Qué beneficio se espera obtener? ¿Existe algún desafío que sea necesario considerar?

► Estadio 4 Análisis inductivo (inducción de conocimiento de casos estudiados)

Derivar guías para guiar la implementación de cualquier pregunta de investigación (RQ) en el futuro (definir un protocolo de investigación/programa de investigación basado en el marco de evaluación ADVANCE) ha sido identificado como el objetivo final de la evaluación de POC. Moverse de casos específicos de POC a una generalización más amplia requiere la investigación y análisis de un número de casos de investigación (POCs) para derivar escenarios básicos.

En resumen, el marco de evaluación ADVANCE ofrece áreas de evaluación, indicadores de calidad, métodos de medición y un plan de tiempo.
2. Development of POC study Evaluation Framework

The principles outlined in the KDC Framework were used to inform and shape the POC evaluation strategy (POC Evaluation framework). A dedicated workshop was organised at Surrey University (8-9, March 2016). Aim of this workshop was to set the context of the evaluation work, by reviewing the project’s objectives, processes, documentation, and progress. The workshop brought together a group of knowledgeable persons from academia and industry, taking part in relevant tasks in the context of the ADVANCE project. Four senior scientists from academia and two experts from the pharmaceutical industry were involved in the discussions.

The defined **objective of POC evaluation** is to demonstrate that the selected POC cases can be implemented effectively using the ADVANCE framework, and to “assess the level of attainment of the ADVANCE mission (and vision) statements, through collecting, analysing and reporting on the outputs of the POCs”. The discussion was aligned with the **value (attainable benefit) dimension** of the KDC Framework. **Feasibility and effectiveness** of the RQ investigation process stand at the centre of the KDC Framework, while the implementation of any research investigation (combinatorial, exploratory or transformational) is also foreseen (**generalisability**). On this ground, during this meeting it was agreed that a structured approach to the evaluation of the outcomes and processed of POC studies is needed. In line with the KDC Framework, a value-based approach was adopted, proposing the use of four stages of analysis, based on the value generated (Figure 28).

![Figure 28. Incremental stages of POC study evaluation](image)

Value is assessed according to the following criteria: Scientific validity and innovation; Process performance and IT infrastructure; Quality standards, regulatory compliance and legal
robustness; and Stakeholder satisfaction and Code of conduct. This analysis will be considered for defining the indicators and the processes of the evaluation framework.

2. POC1 study evaluation results

Two rounds for POC evaluations are planned, each focusing on a different POC study. Each round will be conducted in three main steps which are as follows: (1) Evaluation plan definition based on the POC evaluation framework (identification of focus Area, Dimensions, parameters, indicators, questions etc.); (2) Data collection and analysis; and (3) Reporting (findings and recommendations). As the POC framework is a reference document, during each round relevant areas of evaluation, dimensions, and parameters will be identified and questions will be formulated and/or adapted to the scope of the POC study. The first Evaluation Survey for POC1 study (Evaluation Survey 1) was released in August 2016, and responses were collected until early September 2016. This Survey covers indicators on ADVANCE processes, workflows and methods, including questions about acceptability, capability, governance, effectiveness, stakeholder satisfaction and added value. This makes this survey of particular interest to KDC Framework. Results provided formative insight and revealed areas of potential improvement to be considered for the refinement of the Knowledge Discovery Cube Framework. In total, 12 questions were asked. Questions 1 to 6 were used to collect information about respondents, while questions 7 to 12 referred to ADVANCE processes and methods. A total of 36 responses were received from among ADVANCE partners and Associate partners. The overall response rate was 17.4 %. The response by stakeholders group was: academia 18%, public health 21%, regulators 8%, MAH 20% and SMEs 14%. The summary of the results are as follows:

Table 36. Results from POC1 study evaluation.

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Acceptability</th>
<th>Satisfaction</th>
<th>Transparency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acceptability of processes and workflows in ADVANCE</td>
<td>30.65% (data sources approval), 33.4% (data source selection) to 72.2% (choice of research teams members)</td>
<td>23% (speed), 17% (credibility), 35% (IT capacity), 58% (Usefulness), 55% (Innovation), to 72.3% (Enabling stakeholder collaboration)</td>
<td>52.78% (16.67% fully transparent and 36.11% transparent) to 33% partially transparent</td>
</tr>
</tbody>
</table>

The ADVANCE framework capability to enable and facilitate public-private and public-public collaboration the agreement level is 69.44%, and only 8.33% of the respondents said they don’t know about the collaboration.

Data protection, privacy and security, 47% selected acceptable, 6% slightly acceptable and code of
conducted response shows 61% acceptable, 8% slightly acceptable and 17% replied that they don’t know. For databases characteristics percentage (%) of unsure was very high i.e. 59% speed, 59% accuracy and 59% credibility. Similarly 50% were unsure about IT capacity, 49% availability, 30% flexibility, and 36% for both usefulness and innovation. In certain cases the respondents could not reply i.e. for data approval overall 41.7% replied that they don’t know and 13.9% selected neutral.

Responses were also analysed with regards to the respondents’ role in the project (e.g. members of Steering Committee), stakeholder type (e.g. SME) etc, with rates showing no significant deviation from average. The preliminary evaluation results were communicated to the project’s Steering Committee and General Assembly, during two meetings that took place in September and October 2016 respectively. During a dedicated workshop that was organised in the context of the General Assembly meeting in Barcelona (POC Evaluation session, October 5, 2016), participants emphasised that the decision making process regarding POC studies needs to become more transparent, with regards to database selection (criteria of database selection, selection of decision makers and their qualifications etc), the selection of methods, etc.

Subsequent POC studies should speed up the pathway from “POC-setup” to “POC run” (i.e. topic selection, protocol development, regulatory PASS+/PAS, database selection, data extraction, POC implementation, etc). They also stressed the need to evaluate the quality of the collaboration, i.e. the quality of interaction among ADVANCE stakeholders taking part in the POC study, and called for more qualitative/descriptive feedback to be collected, also from “external to the POC evaluation” reviewers (e.g. industry representatives), as a means to improve the quality of the evaluation process. Responses can be considered encouraging at this stage of the project, given that the development of the ADVANCE platform is ongoing. Nonetheless, respondents expressed their concern regarding specific aspects. By assessing the existing conditions of POC1, evaluation (Survey 1) identified strong and weak points in the implementation of the study process, which need to be made actionable. Recommendations need to be derived, in order to develop opportunities for future improvement.

To facilitate sense making, in the context of the present research work these results were reviewed and analysed from the perspective of the Knowledge Discovery Cube Framework. The KDC Framework considers Research Investigations (RIs) as being constantly in a state of “imperfect development”, with evaluation and foresight shaping the ground for continual improvement and innovation. In the case of ADVANCE it is also imperative to close the loop between POC study implementation and POC study design, i.e. derive improvement actions
from the evaluation results. To produce actionable insight, performance indicators were mapped on individual process phases, as a means to identify areas of potential improvement, important aspects to be considered for the standardisation of the POC1 study or for the setup of future POC study processes.

Table 37. Mapping of selected indicators and POC1 study results to process phases

<table>
<thead>
<tr>
<th>Indicator ID</th>
<th>Evaluation area (What?)</th>
<th>Dimension (What?)</th>
<th>Indicator (What?)</th>
<th>Scoping</th>
<th>Protocol writing</th>
<th>Data extraction</th>
<th>Data Transformation</th>
<th>Analysis</th>
<th>Reporting</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>Process</td>
<td>Acceptability</td>
<td>Acceptability of study proposal, workflow, and overall implementation of the process - report by stakeholders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Definition of Research question and choice of Benefit/Risk scenario</td>
<td>55%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Choice of study research teams members</td>
<td>72%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Protocol development</td>
<td>Protocol development</td>
<td>60%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Protocol review</td>
<td>Protocol review</td>
<td>58%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Protocol approval</td>
<td>Protocol approval</td>
<td>50%</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Data source selection</td>
<td>Data source selection</td>
<td>33%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Data source approval</td>
<td>Data source approval</td>
<td>30%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Data storage code of conduct</td>
<td>Data storage</td>
<td>52.80%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Data protection, privacy and security</td>
<td>47.20%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>Quality</td>
<td>Compliance</td>
<td>Legal approval of study</td>
<td>yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>Process</td>
<td>Transparency</td>
<td>Transparency EMA definition?</td>
<td>52.76%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>Stakeholder satisfaction</td>
<td>Transparency</td>
<td>Transparency ECDC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results referring to specific process phases were aggregated. Table 38 summarises items referring to the process scoping phase that received lower scores and can be characterised as “weak points”. Weak points represent potential areas of improvement.

Table 38. Selected evaluation results for the process scoping phase.

Acceptability of study proposal, workflow, and overall implementation of the process - report by stakeholders
Definition of Research question and choice of Benefit/Risk scenario: 55%
Data source selection: 33%
Data protection, privacy and security: 47.20%

Transparency ECDC
Improved access to data: 26.47%
Ability to identify databases and review their characteristics in terms of speed: 23.53%
Ability to identify databases and review their characteristics in terms of accuracy: 23.53%
Ability to identify databases and review their characteristics in terms of credibility: 17.65%
Flexibility to address any vaccine benefit/risk questions: 24.24%

Performance indicators referring to the study scoping phase (planning stage) provide an indication of whether or not the preconditions for the execution of a scientifically and
operationally valuable study that complies with legislation, relevant codes of conduct etc, are met. The participants of Evaluation Survey 1 expressed their concerns mostly about the “fingerprinting” exercise with regards to database selection and data quality, accuracy, speed and availability. These points represent potential areas of improvement.

3. ADVANCE Evaluation Workshop (London)

The results of the POC1 evaluation were presented and discussed during the ADVANCE Evaluation Workshop, organised in London (15 December 2016), which involved ten participants: (a) experts in Information Systems and Clinical Informatics; and (b) senior scientists in the fields of pharmacology, pharmaco-epidemiology, pharmacovigilance, risk assessment, etc, from academia, public health organisations, regulators, the pharmaceutical industry and SMEs. Furthermore, the Workshop involved representatives of all relevant Work Packages: WP1 (“Best practice and code of conduct for benefit-risk monitoring of vaccines”), WP3 (“Data sources for rapid and integrated benefit-risk monitoring”), WP4 (“Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit-risk monitoring”) and WP5 (“Proof-of-concept studies of a framework to perform vaccine benefit-risk monitoring”). All participants had a good overview of the work of the ADVANCE project, with some being members of the project’s Steering Committee, or leading project work in specific areas (Work Package Leaders).

Discussing the results of the POC1 evaluation with regards to database fingerprinting, participants noted that concrete criteria exist to guide database selection and that this exercise spans several dimensions, beyond data extraction and retrieval (technical), namely: (a) Data quality and suitability to answer the research questions of the study; (b) Approval issues (organisational); and (c) Ethics and privacy concerns regarding data use. Strategic decisions made with regards to the organisation of a POC study can affect the perceptions of participating stakeholders. For example, rather than transferring to the RRE platform the data in their original form (i.e. as stored in their originating database), local databases export data in a common file format using a script prepared by the statisticians for this purpose. It is important that statisticians receiving and aggregating these datasets feel “comfortable” with this data to answer the research questions of the POC study. However, **statisticians have less detail about the data and cannot go back to the original dataset to check results in case of doubt. They cannot always be**
certain that the extraction and transformation of data into the common file was without loss of quality.

During this meeting the first version of the ADVANCE process map was presented, drawing from the KDC Framework and in response to the findings of the first POC study. Discussing the development of process models for the POC study, advantages were identified on both the strategic and the operational level. From a strategic point of view, this analysis can help devise plans to improve and accelerate POC process design, including the identification of reusable modules. Furthermore, it allows for an early “study of the POC study” during the scoping phase, to assess its feasibility and anticipate potential barriers in its implementation. On the tactical level, the use of process models allows to improve POC study implementation: the launching and putting into practice of POC studies. It can further help improve tools and methods. Recommendations were also made regarding the contents of the process map (e.g. addition of a “protocol storing/archiving” process to the protocol writing phase).

The central role of database fingerprinting to the study process was discussed. Participants noted that while database fingerprinting was performed with on in parallel to the scoping phase of the POC1 study, fingerprinting is essentially an autonomous support function and should be modeled as a separate and reusable process to support all subsequent POC studies.

It was agreed to elaborate further on the lessons learned from the POC1 study to derive recommendations and critical points to consider for the planning of the second POC study. It was also agreed to approach the design of the POC2 study as a process.

4. Discussion

Evaluation is focused on both the outcomes (vertical dimension) and the work processes (horizontal dimension) of a POC study. Given the importance of evaluation, to ensure its success, the following criteria were set for the POC evaluation design:

- A logic process/model to identify appropriate methods that are fit for purpose.
- Covering the whole process of implementing the POC study – not only the outcomes, but how these were achieved.
- Enough flexibility to accommodate complexity while retaining clarity of aim.
- Conduct the evaluation in phases, aiming to capture information at the most effective point(s) in time.
To accommodate these requirements the Evaluation Framework needs to (a) build on a comprehensive view of the POC study and (b) be complemented by suitable instruments to enable action taking in response to issues identified, towards the resolution of problems and for improving the implementation of POC studies. The KDC Framework offers a global picture of the RI process as integrated within the research knowledge production and application cycle. Feasibility and effectiveness of the research investigation process stand at the centre of the framework, being viewed from a different angle throughout the RI life-cycle. An Optimisation and Innovation dimension is also included to close the cycle. The outcomes of the evaluation of the first POC study revealed the need to make these features of the KDC Framework actionable for POC study planning, implementation and monitoring. A generic reference model for the instantiation of ADVANCE POC studies was developed based on the present research to support the design and execution of the study process and facilitate understanding among involved stakeholders. It is presented in Part C of this Chapter.
1. The ADVANCE generic reference model

In the case of vaccines research, de novo information generation about the burden of disease, vaccine utilisation, benefits and/or risks of vaccines may generally follow a generic study flow comprising study scoping and protocol writing, data extraction, data transformation, analysis and reporting. The ADVANCE POC studies build on distributed collaborative information generation workflows, with common protocol, standardised transformation and shared analyses while data extraction and original data remain local. The KDC Framework, outlined in Chapter 4 (Part B), is a theoretical framework that delineates causal and explanatory relationships and provides practical references for the instantiation of Research Investigations and the incorporation of emerging domain knowledge and technological innovation. Instantiations operationalise constructs, models, and methods. Building on the KDC Framework a generic reference model for the instantiation of ADVANCE POC studies has been developed to support the design and execution of the study process and facilitate understanding among involved stakeholders. A process model is the indicated method for this, according to Curtis et al. (1992) process models: (a) facilitate human understanding and communication, (by providing common representational format); (b) support process improvement (by providing a basis for defining and analysing processes); (c) support process management (by allowing for actual project behaviours comparison); (d) automate process guidance (by providing automated tools for manipulating process descriptions); and (e) automate execution support (allow for controlling behaviour within an automated environment).

Instantiation is about designing, sourcing and implementing concrete study protocols, utilising specific resources and available capabilities to achieve sub-goals that support the defined objective of the study. Beyond its tactical (operational) application, the ADVANCE reference model can be further utilised as a strategic thinking instrument to identify clear and broader goals that advance vaccine benefit/risk studies. A typical research process contains the following steps: (1) Formulation of the research questions or hypothesis to be tested; (2) Investigation of the feasibility of the research; (3) Design of the research process; (4) Collection and preparation of data; (5) Data analysis; and (6) Reporting. The ADVANCE generic reference model for the
instantiation of POC studies comprises the ADVANCE reference process map and the process planning canvas. The two instruments, which reflect the operationalisation of the KDC Framework constructs, models, and methods, are detailed in Sections 1.1 and 1.2. Section 3 details empirical validation activities referring to the ADVANCE generic reference model.

1.1 ADVANCE reference process map

In the framework of ADVANCE, a benefit/risk study process typically involves six phases: study scoping, protocol development, data extraction, data transformation, analysis & reporting, and evaluation. To ensure that it is sufficiently generic and applicable in various investigations (vaccine studies), the reference model developed for the ADVANCE project is conceptualised as a matrix. While in this model research is depicted as a sequential process involving several discrete steps, there are many possible paths through this matrix, depending on the specific needs of each study. The completion of each step before proceeding to the next is not always mandatory: some steps may be executed in sequence, while others can be carried out simultaneously. Iterations between steps and/or step omissions are also possible. Despite these variations, the idea of a linear sequence is useful for planning and managing the implementation of a study project. The process model (reference process map) created for the purposes of developing and managing the ADVANCE POC studies comprises three levels: (a) Level 0, the POC process; (b) Level 1, the six phases of the POC study process; and (c) Level 2, the sub-processes within each phase. A diagram showing the four phases (Level 1) and sub-processes (Level 2) is illustrated in Figure 29. Sub-processes do not have to be followed in a strict order. Some iterations of a regular process may skip certain sub-processes.

Protocol development starts with scoping: shaping of the information that is needed to develop the objective and design, as well as feasibility assessment. Scoping is the first step prior to protocol writing which in itself comprises of several steps from writing the protocol, defining outcomes, covariates and exposures, as well as obtaining approvals and registering of the protocol. Data extraction is the step where queries are launched on the original data source to retrieve study specific data (e.g. the vaccinations of interest, the population of interest for the study). Data transformation is the step during which the extracted data are transformed into an analytical dataset in line according to the study design: e.g. a cohort study requires transformation of the data into a record per patient with start and end of follow-up of that patients’ time. Analysis comprises of describing the data and further analysing them according to
a statistical analysis plan. Tables are created and a report delivered. In the analysis phase a statistical software is used to calculate the predefined estimates.

Figure 29: ADVANCE reference process map

It should be further noted that, while the hereby presented instantiation of the ADVANCE model is descriptive (Bell & Raiffa, 1988), the ultimate objective is to facilitate prescriptive and/or comparative applications, in line with the project’s aim to develop a production pipeline for vaccine benefit/risk studies. This can be achieved by means of the subsequent POC experimentations scheduled in the project. According to De Bruin et al. (2005) a descriptive model allows stakeholders to develop a deeper understanding of the "as-is" domain situation and after it is applied a few times, the descriptive model can be further developed to become prescriptive and concrete maturity levels can be defined. A prescriptive model provides emphasis on the domain relationships to business performance and indicates how to approach maturity improvement in order to positively affect business value, i.e. it enables the development of a roadmap for improvement (De Bruin et al., 2005). In its comparative sense the model will enable
benchmarking vaccine benefit/risk studies and allow for example to compare similar practices for different vaccines. For this reason, particular emphasis has been placed on the evaluation work and the definition of KPIs.

The KDC Framework stresses the importance of collaboration, stating that a Research Investigation (in the present context a POC study) is essentially a Knowledge Management exercise that builds on knowledge contained in both information sources and people. Capabilities therefore need to be examined from both perspectives, as they entail both an information management and a behavioural aspect. In this light, an important dimension of the ADVANCE model is the identification of Collaboration Impact Zones. Collaboration impact zones are defined by the Collaboration Consortium (2010) as “those junctures where interactions and the exchange of expertise and information are frequent, urgent, and complex: these may be focused on either internal or external collaboration”. They allow stakeholders focus on the right areas of collaboration to ensure that the benefits of collaboration is maximised. In the present context, collaboration impact zones are located in the external operations of organisations that take part in the POC study in any role or capacity, but analysis can be further detailed to illuminate internal collaboration impact zones, marking the internal (e.g. interdepartmental) collaborative work that supports the investigation. For a POC study, it is a key challenge to enable information integration, knowledge sharing, and connectivity between people, so as to facilitate the sharing and use of unarticulated knowledge. Knowledge sharing and collaboration tools need to be implemented and aligned with the requirements of the different collaboration impact zones in the context of individual processes of the POC study. Collaboration helps leverage knowledge and skills throughout the network (ecosystem) of participating stakeholders. Depending on the overall maturity of the study (i.e. its level of systematisation) and the requirements of individual processes, collaboration may be of a structured or of an investigative type, or a combination of the two. The effectiveness of vaccine study collaborations may be assessed in terms of the criteria defined by the Collaboration Consortium (2010): reach (ability to reach the right experts and/or communities), richness (ability to tap into information or expertise that is not easily available) openness (ability to bring the best people into the study process and to collect the best-quality inputs), and speed (shorten the cycle time to complete the study and produce results).
Aim of the developed process mapping (and workflow) is to provide a comprehensive overview of the top level process of vaccine benefit/risk study implementation, and to facilitate its operationalisation through the identification and mapping of relevant capabilities. In this light the reference model brings together and incorporates several tools and processes already defined by the ADVANCE project: Good practice guidelines, Code of Conduct and Collaboration, Ethics and Privacy, and data protection) to feed into the overall ADVANCE research process. The reference model describes the process from study inception to protocol approval and execution, also including performance indicators, to allow for performance analysis and the formulation and interpretation of recommendations.

1.1.1 Phases of the ADVANCE POC study workflow

The POC study process flow typically involves study scoping and protocol writing, data sourcing, data extraction, data transformation, analysis, archiving and reporting. An additional process was added for output evaluation and compliance assessment. The evaluation process covers the evaluation of outputs and outcomes, and compliance to the regulations and Code of Conduct. The supporting processes cover Rules of Governance, Code of Conduct, Collaboration, and Ethics and Privacy. A POC study typically goes through two main stages (Figure 30): planning and implementation. Planning is a preparatory stage that includes study scoping, feasibility assessment and protocol writing. Implementation involves sourcing (data collection, cleaning and extraction) and execution (data transformation, processing, interpretation and analysis). Work is complemented by evaluation and other support activities.

Figure 30. Stages of a POC study

Evaluation work is focused on both the outcomes and the processes of the study. This includes both the Work Processes (i.e. generic activities addressing study operations during individual
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stages and as a whole (horizontal dimension)) and the Outputs (i.e. the results of the POC study, including intermediate outcomes (vertical dimension)). Evaluation defines quality and performance criteria and indicators that permeate the entire study process. Failing to meet the quality requirements or standards can have negative consequences on the success of the POC study. Based on the above categorisation, process indicators referring to processes in the planning stage are used to assess the feasibility of the study, i.e. to examine whether or not the preconditions for the execution of a scientifically valuable study that complies with legislation, relevant codes of conduct etc, are met. The POC evaluation is therefore based on the systematic assessment of whether the concept designed and tested through conducting the proof of concept is acceptable and good to be recommended for release into production, in the ultimate project final blueprint. Overall, the vision statements highlight several objectives: Best evidence (scientific validity); Right time (faster than current state of the art); Integrated (multiple stakeholders, multiple data streams, benefit and safety combined); Ability to perform monitoring (infrastructure and methods); Clear governance rules (code of conduct, ethics, data protection, regulatory and legal compliance, transparency); and meeting common interest (stakeholder satisfaction).

The layout of the generic processes is shown in Figure 36. To ensure that it is a sufficiently generic instrument and applicable in various POC studies, the generic process model is conceptualised as a matrix. While in this model work is depicted as a sequential process involving several discrete steps, there are many possible paths through this matrix, depending on the specific needs of each study. Furthermore, the completion of each step before proceeding to the next is not always mandatory: some steps may be executed in sequence, while others can be carried out simultaneously. Iterations between steps and/or step omissions are also possible. The generic process map is intended to facilitate the investigation of POC studies from different perspectives and at different levels of analysis. Overall, four interrelated perspectives (Curtis et al., 1992) underlie the generic process map:

- **Functional** represents what process elements are being performed, and what flows of informational entities (e.g., data, protocols etc), are relevant to these process elements.

- **Behavioural** represents when process elements are performed, their sequencing, potential feedback loops, iterations, etc.
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- **Organisational** represents where and by whom (which actors) in the network of participating stakeholders process elements are performed, the physical communication mechanisms used for transfer of entities, and the physical media and locations used for storing and archiving entities, etc.

- **Informational** represents the informational entities produced or manipulated by a study process. This includes data, artifacts (e.g. study protocols), outputs (intermediate and end), and other objects (e.g. support documents).

In Figure 31, the processes in the ADVANCE reference process map are colour-coded according to their relevance to work teams (violet), scientific integrity (green), data privacy (blue), DB fingerprinting (orange), and reporting/publication and main processes (yellow). In terms of Collaboration Impact Zones, the different work teams formed throughout the process to organise and manage/execute different process phases represent the critical knowledge exchange junctures of the POC study. Teams may involve domain experts, data custodians, statisticians etc. from different organisations. Their composition, tasks and objectives, collaboration methods and means employed conditioned by the needs of the POC study in the respective process phase.

![Figure 31: extended ADVANCE reference process map](image-url)
In the above illustration the ADVANCE reference process map is further extended to include milestones, support processes reference and support artefacts, reusable artefacts and information technology tools.

1.1.2 Milestones

A typical POC study process comprises the following set of Milestones. A different set of Milestones may be defined to better describe alternative study paths.

<table>
<thead>
<tr>
<th>Table 39. Milestones of the POC study process</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1: The proposed study has been investigated and is feasible in the present context.</td>
</tr>
<tr>
<td>M2: A formal study protocol has been developed.</td>
</tr>
<tr>
<td>M3: The data needed for the study has been extracted and collected, as specified in the protocol.</td>
</tr>
<tr>
<td>M4: The collected data has been integrated and processed.</td>
</tr>
<tr>
<td>M5: The results of data analysis have been interpreted.</td>
</tr>
<tr>
<td>M6: A report/publication of the scientific conclusions or any other relevant artefact to communicate the results has been prepared, controlled and approved.</td>
</tr>
<tr>
<td>M7: The quality of the study has been evaluated (scientific validity of results, quality of the procedure). Compliance with the Code of Conduct has been confirmed.</td>
</tr>
</tbody>
</table>

1.1.3 Main Processes

(i) Scoping process

Scoping is the starting point of the process following the submission of a proposal/request for a B/R study to be organised. The scoping phase comprises an investigation of the study’s required capabilities and value prospects, and is aimed at determining the study’s feasibility. The early discovery of potential capability gaps between the current (available) and the desired (required) capabilities of the study is critical for its success. By analysing the differences, actions can be taken to eliminate the capability gap and the experts’ team can proceed to describe in detail the scope of the POC study, the research questions and the expected outcomes.

(ii) Protocol development

The Protocol development phase is about preparing a formal protocol to guide the execution of the POC study. Relevant existing protocols may be reviewed and adapted to the scope of the present study. Depending on the type of study, standardised procedures and relevant guidelines need to be followed. This includes reviewing and obtaining approvals and registering of the protocol in line with the guidelines that apply for the specific type of study (EU pass register).
(iii) Data Extraction
Data extraction is the step where queries are launched on the original data source to retrieve study-specific data (e.g. the vaccinations of interest, the population of interest, outcomes etc). As data comes from heterogeneous sources, the quality of the data source is checked against relevant quality parameters and criteria. Quality requirements typically include reliability, transparency, coverage, validity, interoperability, harmonisation, coding and compliance with relevant legislation, directives and regulations.

(iv) Data Transformation
During the data transformation phase the extracted data is transformed into an analytical dataset, in line with the study design: e.g. a cohort study requires transformation of the data into a record per patient, with start and end times of patient follow-up. Datasets are subsequently transferred to the central platform for analysis.

(v) Analysis and Reporting
During the analysis and reporting phase a team of data analysis experts aggregates datasets coming from different sources and analyses the cumulative set according to the defined statistical analysis plan. Tables and Figures are created and documented, and a report is delivered as a final output. In the analysis phase, a statistical software is used to calculate a set of predefined estimates. This step also covers the report delivery and the registration of the reports in EU PAS register.

(vi) Evaluation
Evaluation starts with the identification of the important areas of evaluation and the selection of relevant performance indicators and parameters. Relevant data (both quantitative and qualitative) regarding the study process and the results produced is collected and analysed. The findings can provide feedback for improvement. In line with the scope of ADVANCE to establish a reliable, valid and tested framework to rapidly provide robust data and scientific evidence on vaccine benefits and risks, an important set of guidance documents was produced, addressing Code of Conduct, Rules for Governance, Best practices guidelines, Collaborations, Data protection guidance, IT tools and DB fingerprinting issues. The KDC was applied to put this reference documentation into perspective, linking guidance with the study implementation process and the involved capabilities to subsequently identify potential areas of systematisation and to facilitate
the transformation of POC experiments into standardised practices and the overall the scaling of the ADVANCE framework.

1.1.4 Supporting Processes
Looking at the systematisation potential of ADVANCE, the following supporting processes are defined:

(i) Database Fingerprinting
In the ADVANCE project “fingerprinting” represents a critical task for determining the suitability and quality of evidence sources. It included a set of quality control activities to produce a standard, automated description of observational healthcare database contents in order to understand data quality and appropriateness for vaccine benefit/risk studies. As a support process Database Fingerprinting is about the creation and maintenance of a record of fingerprinting results to be revised when changes occur (changes in existing databases, addition of new databases). The need to define two additional support processes stemmed from our analysis as potentially useful for the “production” version of the ADVANCE system.

(ii) Stakeholder profiling
Stakeholder profiling is intended as an inventory of individual experts (domain experts, statisticians, evaluation experts, etc) to be consulted for the selection of members during the creation of working teams. In addition to the area expertise and to affiliation, information related to participation clearance (conflict of Interest, compliance with ethical conduct etc) can be included, to speed up the team formation. Similarly to the above, the stakeholder profiling records need to be maintained and updated.

(iii) Governance
Depending on the POC study, different governance structures may be applied. The support process is intended for the rapid alignment of the work teams organisation and operations to the governance principles that apply.

1.1.5 Artefacts
Another important aspect of ADVANCE are internal and external reference materials, supporting documentation, and reusable artefacts produced at different stages of the study process (Figure 32).
1.2 ADVANCE Process Planning Canvas

While the reference process map provides an overview of the POC study process and an indication of the principal capabilities required, it lacks the level of granularity stipulated by the KDC Framework. An additional planning instrument that can be used for the organisation of each phase of the study and of the study as a whole, to allow for the combined investigation of data, methods and capabilities is the process planning canvas. The concept is an adaptation of the Business Model Canvas (a strategic management and lean startup template for developing new or documenting existing business models). Its aim is to help identify and provide an overview of the important building blocks of each phase and their interdependencies. It can also be applied to provide a cumulative view of structural elements of the entire study process.

![Figure 32: Process planning canvas](image)

The elements included in the process planning canvas (Figure 32) are defined in Table 40:

<table>
<thead>
<tr>
<th>Element</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope</td>
<td>The scope of the phase/process</td>
</tr>
<tr>
<td>Value proposition</td>
<td>The objectives and expected achievements upon completion of this phase/process</td>
</tr>
<tr>
<td>Metrics</td>
<td>Key Performance Indicators regarding the outcome(s) of the phase/process and the execution of the phase/process</td>
</tr>
<tr>
<td>Tasks</td>
<td>Key activities performed during this phase/process</td>
</tr>
<tr>
<td>Data</td>
<td>data sources used for the purposes of this phase/process</td>
</tr>
<tr>
<td>People</td>
<td>People as actors performing tasks as part of the POC study. Issues to be investigated include knowledge, skills, motivation (in case of direct reporting by patients), as well as conflict of Interest issues, data clearance permissions etc.</td>
</tr>
<tr>
<td>Technology &amp; tools</td>
<td>All the equipment and tools required for the execution of tasks. It comprises infrastructure and tools spanning the entire digital knowledge value chain: data collection &amp; reporting tools, data storage, retrieval &amp; transfer infrastructure, Data &amp; Text mining tools, Computational tools, Decision Support tools, communication &amp; collaboration tools,</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Element</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organisational issues:</td>
<td>The authority structure, communication and collaboration channels, and workflow within and among participating organisations. It comprises the code of conduct and governance structures, systems, and roles, policy and legal provisions and guidelines.</td>
</tr>
<tr>
<td>Reference &amp; support artefacts:</td>
<td>depending on the case, this may include overarching studies, guidelines and other relevant materials</td>
</tr>
</tbody>
</table>

The first column of the Process planning canvas provides an indication of purpose and value. Upon completion of a process phase/study process, the value proposition and the metrics specified can help determine the realised value of the process phase/study process (i.e. the actual value achieved by the process phase/POC study) and map this to the actual capabilities, data and methods employed. This can help identify potential performance or innovation gaps in the process phase/study process and support subsequent targeted improvement efforts.

The second column describes the capabilities needs of the process phase/study process. In the present context, People, Technology & tools and Organisational issues jointly constitute the capabilities of a POC study, i.e. the contextual, situational factors that affect the implementation of the POC study, conditioning performance and actions. The three are interrelated and mutually adjusting variables and have to fit the overall tasks to be performed. For example with regards to the implementation of a new POC study, the following key questions need to be examined in conjunction with the people involved, the technology/tools employed, and the organisational setting:

Table 41. Interrelationships between capabilities

<table>
<thead>
<tr>
<th>Technology/Tools</th>
<th>People</th>
<th>Organisational issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the implementation of a POC study require changes in existing systems and tools, networks and configurations of participating organisations?</td>
<td>Are people competent enough to perform the assigned tasks, use the designated technology/tools? Is training required?</td>
<td>Is the execution of the foreseen tasks permitted according to the organisations’ existing structures and regulations?</td>
</tr>
<tr>
<td>Does this change affect other components of the organisations’ ICT infrastructure?</td>
<td>Does the organisation have to hire new specialised personnel?</td>
<td>Are changes and adaptations in organisations’ structures needed?</td>
</tr>
<tr>
<td></td>
<td>Are there issues of conflict of Interest issues, data clearance permissions etc, restricting a person’s participation?</td>
<td>Do organisations have to revise job positions (new job positions required), job descriptions or personnel allocation (including number of people assigned to each job position) to fulfill the requirements of the POC study?</td>
</tr>
<tr>
<td></td>
<td>Are the people willing to participate? Is additional motivation (incentives) needed?</td>
<td>Are policy revisions or legal reforms required?</td>
</tr>
</tbody>
</table>
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The subsequent two columns describe the tasks performed and the data used, including additional reference of support artefacts. An example of the Process Planning Canvas used to outline the scoping process is illustrated in Figure 33.

![Figure 33. Process Planning Canvas for the study scoping phase](image)

Following is a proposed workflow for the combined utilisation of the two instruments to examine the feasibility of a POC study:

### Table 42. Workflow for the feasibility assessment of studies

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Scope of POC study. Define scope of POC study</td>
</tr>
<tr>
<td>2</td>
<td>Selection of method and data evidence. Identify scientific method and relevant data sources to be used for the purposes of the POC study</td>
</tr>
<tr>
<td>3</td>
<td>Identify process steps. Use the Process Map to map the POC study to relevant process steps. Define POC study workflow.</td>
</tr>
<tr>
<td>4</td>
<td>Map POC study to required capabilities. Identify capabilities required for each phase of the POC study. Fill out Capability Canvas for each stage of the process.</td>
</tr>
<tr>
<td>5</td>
<td>Identify existing capabilities. Examine existing capabilities to assess current strength/performance of capabilities.</td>
</tr>
<tr>
<td>6</td>
<td>Examine Capabilities gap. Assess existing capabilities against the capabilities required for the implementation of the POC study.</td>
</tr>
<tr>
<td>7</td>
<td>Determine feasibility of POC study. Depending on the outcome of the previous step:</td>
</tr>
<tr>
<td></td>
<td>- All capability requirements are fulfilled in the present context (action: proceed with POC study protocol definition).</td>
</tr>
<tr>
<td></td>
<td>- Capabilities gaps can be addressed (action: derive demand strategies from capabilities gap).</td>
</tr>
<tr>
<td></td>
<td>- Capabilities gaps cannot be addressed (action: dismiss POC study or revise selection of method and data sources and repeat process).</td>
</tr>
</tbody>
</table>
The most effective and efficient insight on a POC study is gained through a combination of the two instruments. Improvement and optimisation and can be achieved by doing these exercises repeatedly to enhance and better align existing capabilities and improve operations. Experience shows that starting with the first (process map) is a good way to get an overview of the study and establish a common reference among participants. Then a detailed analysis of the different phases should follow. The next step is to describe the analysis results in process models, detailing how each process phase will be performed. Detailed process model of the study scoping and protocol writing phase developed based on the experience of POC1 are included in Appendix 3. For the creation of these models the Event-driven Process Chain (EPC) methodology was applied, developed in the early 1990’s by the Institute for Information Systems (Iwi) of Saarland University, Germany, as an integral part of the ARIS system (Ryan K.L., Stephen S.G., & Eng Wah, 2009). EPC enables the creation of consistent descriptions and visualisations as well as content- and time-related dependencies for all open corporate tasks. Connections between tasks are based on events that trigger the task and the events the fulfilment of the task itself triggers.

2. Guidance for the implementation of instruments

Moving a scientific B/R investigation method to a distributed, digital environment is a challenging task. When designing the future digital and collaborative way of POC study implementation, the requirements of collaborative “online” execution become the central issue. Essentially a re-engineering of the scientific B/R investigation protocol is done, adapting it to the new form of online study performance. During study modelling, the following items have to be described and defined:

- The workflow of the study process at the central platform (Remote Research Environment, RRE) and the interactions with the back-office (data providers and third parties);
- The data resources required for the POC study;
- All other support data required for the POC study;
- The organisational and legal grounding of the study process (governance, responsibilities, legal prescriptions and legal obligations);
- The input/output and throughput data required at the respective steps during POC study implementation (datasets and relevant data models);
Chapter 5: The ADVANCE case study

- All pre- and postconditions that apply at the different stages of the study process.

Overall Quality check criteria

During the definition of a POC study model on the basis of the Process map, key questions to be asked with regards to the model’s structure and quality include:

Table 43. Quality check criteria

<table>
<thead>
<tr>
<th>Structure of the POC study model</th>
<th>Quality of the POC study model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are all relevant process steps of the POC study identified?</td>
<td>Are the terms employed in the description self-explaining?</td>
</tr>
<tr>
<td>Is the workflow of the POC study modelled correctly?</td>
<td>Is the model’s level of granularity sufficient? If not: add process trees to detail activities</td>
</tr>
<tr>
<td>Are any relevant alternative paths displayed?</td>
<td>Is the use all terms consistent throughout the model?</td>
</tr>
<tr>
<td>Which stakeholder roles are involved in each process step?</td>
<td>Is complexity reduced?</td>
</tr>
<tr>
<td>What is the exact process step–stakeholder role relationship (is responsible, contributes, assists…)?</td>
<td>Is all information relevant for technical implementation displayed?</td>
</tr>
<tr>
<td>What is the objective of the process step?</td>
<td>Is all information relevant for organisational implementation (roles and responsibilities) displayed?</td>
</tr>
<tr>
<td>Which ADVANCE module is used in the process step?</td>
<td>Are all process-related verbal descriptions comprehensive and accurate?</td>
</tr>
<tr>
<td>What other socio-technical capabilities are required for the process step?</td>
<td></td>
</tr>
<tr>
<td>Where do relevant data come from? Where do they go next?</td>
<td></td>
</tr>
<tr>
<td>What data is used as input in the process step? What output data is produced?</td>
<td></td>
</tr>
</tbody>
</table>

4.2.2 Compliance

Specific guidelines apply and need to be accommodated at various stages of the process. Following is an indicative catalogue of guidelines of relevance to pharmacovigilance:

Table 44. Guidelines for compliance

<table>
<thead>
<tr>
<th>Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADELF Recommendations for professional standards and good epidemiological practices (Version 2007)</td>
</tr>
<tr>
<td>AGENS, DGSPM and DGEpiGPS – Good Practice in Secondary Data Analysis</td>
</tr>
<tr>
<td>EMA, Policy on the handling of conflicts of interests of scientific committee members and expert</td>
</tr>
<tr>
<td>EMA, Guideline on good pharmacovigilance practices (GVP) Module VIII - Post-authorisation safety studies</td>
</tr>
<tr>
<td>EMA, Guideline on good pharmacovigilance practices (GVP)-P.I: Vaccines for prophylaxis against</td>
</tr>
</tbody>
</table>
Qualitative feedback with regards to the ADVANCE generic reference model for POC study instantiation was collected at various points of the project work. In the following sections significant instances of explicit feedback collection are outlined.

3. ADVANCE Evaluation Workshop (London)

The first formal presentation of the ADVANCE process map took place during the ADVANCE Evaluation Workshop, organised in London (15 December 2016), which is detailed in Section B.3 of the present Chapter. The need for a formal planning instrument had emerged from the findings of the POC1 evaluation. During this meeting the first version of the ADVANCE process map was presented, drawing from the KDC Framework and building on lessons learned from POC1 study, particularly with regards to issues of speed and timeliness, and transparency and collaboration. Discussing the development of process models to guide the instantiation of POC studies, advantages were identified on both the strategic and the operational level. From a strategic point of view, participants agreed that this analysis can help devise plans to improve and accelerate POC process design, including the identification of reusable modules. Furthermore, it was acknowledged that this approach allows for an early “study of the POC study” during the scoping phase, which enables to assess the feasibility of the study and anticipate potential barriers in its implementation. On the tactical level, the use of process models allows to improve POC study implementation: the launching and putting into practice of POC studies. It can further help improve tools and methods.

Subsequently, dedicated focus group discussions were organised to elaborate further on the ADVANCE process map and the process planning canvas.
4. Focus group with POC study leaders

Following is a presentation of the dedicated focus group discussion with the participation of POC study leaders and members of WP5, organised on February 8, 2017, to **review the instruments and methods developed for the planning of the second POC study on the basis of the KDC Framework operationalisation and the framework at large**. The aim of summative validation is to validate and enhance the data through a focus group consultation process, as part of which selected experts from ADVANCE were invited to participate and review the outputs. The follow-up focus group meeting organised on March 8, 2017 is not reported in the present Thesis.

4.1 Why focus group for the final evaluation?

While focus groups cannot provide statistical data to project to a population, this method is particularly useful when looking for qualitative feedback that will facilitate sense making (O’Donnell, 1988). Aim of validation is to examine the comprehensiveness and fitment of the KDC Framework, identify potential deviant cases and other shortcomings of the present framework from a pragmatic, implementation-oriented perspective. Furthermore, at this stage of work, a focus group discussion was deemed more appropriate (for example compared to individual interviews) given that this technique allows participants to build on and complement each other’s comments and reactions. This can yield synergy of discussion around topics or themes. Earlier work in the context of the ADVANCE project was aimed at providing **empirical insight** into the KDC Framework, namely by studying the practical implications of vaccine safety studies, understanding the factors that affect their success, and learning from the experience of the project participants during their effort to plan, implement the first POC study and draw conclusions to inform subsequent POC experimentations. As described above, insight was collected from a wide range of project documents and from the work of the different communities of stakeholders (project working groups), in a very inclusive manner that combined quantitative and qualitative instruments (survey and work meetings, workshops, etc).

4.2 Why this focus group composition?

The earlier (formative) stages of the case study built on a **horizontal** approach that covered the wide community of ADVANCE stakeholders, irrespective of there being a direct connection between their specific area of work and the research objective. This work revealed the need for
the development of instruments to guide POC study instantiation and monitor its
implementation. The summative validation, pursued through dedicated focus group discussions,
aims to draw specific conclusions on the ADVANCE generic reference model and the
underlying KDC Framework. For this reason, a targeted selection was made. For this reason, a
targeted selection was made. Participants were purposely selected from the task group built
within the ADVANCE project for the selection, planning and implementation of POC
experiments (POC study leaders) and from the POC study evaluation work group (WP5). In
total, eight experts participated in the first Focus Group meeting. The participants were
Information Systems and Clinical Informatics scientists and domain experts (senior scientists in
the fields of pharmacology, pharmacoepidemiology, pharmacovigilance and risk assessment,
etc.) from academia, public health organisations, regulators, the pharmaceutical industry and
SMEs, responsible for the organisation and validation of POC experiments (POC studies). These
experts represent the key informants to involve in the focus group aimed at a comprehensive
evaluation of the Framework, so as to ensure the validity (trust and confidence) of its findings.
The evaluation of the KDC Framework addresses three important dimensions: (a) validity and
comprehensiveness, (b) applicability and usability and (c) added-value.
Morgan (1996) notes that when using focus groups as the primary means of collecting qualitative
data (self-contained use) a careful matching of the goals of the research with the data that the
focus group can produce to meet these goals is required. In the context of ADVANCE there exist
several dedicated work groups. Focus group participants are selected because they share certain
characteristics that relate to the topic of interest (Krueger & Casey, 2014). In line with the
recommendations of Cohen et al. (2002), the following criteria were considered for selecting
informants: (a) status of the informants within the ADVANCE project; (b) closeness to the issue
studied; (c) knowledgeability and competence to pass comments; (d) reliability; (e)
representativeness of the nuances of the issue studied; (f) relationship to other members in the
ADVANCE group. With the KDC Framework being intended as a strategic planning,
instantiation, maintenance and optimisation instrument for medicines and vaccine safety studies,
the involvement of these key informants can provide valid assessments of value to the present
research study. This selection of focus group participants has several advantages:
● This team of experts has a broad overview of vaccine safety studies and their characteristics,
  having performed a thorough review of the area at the onset of the project in search of POC
study candidates. Therefore, they are in the position to **generalise, and/or identify potential deviant cases.**

- POC study leaders have been responsible for the design and implementation of the first POC study, which, while it had a clear scientific outline, was faced with significant **challenges** being the first instantiation of the ADVANCE prototype platform. Therefore, this team of experts can identify potential shortcomings of the KDC framework speaking from a **pragmatic, implementation-oriented perspective.**

- Members of the POC study evaluation workgroup (WP5) have been responsible for the evaluation of the first POC study.

The meeting, organised on February 8, 2017, was held online (via teleconference) and the views of the participants were collected using written notes. Krueger & Casey (2014) stress the importance of creating a permissive environment that encourages participants to share perception and points of view. In the present case, this was further facilitated by the fact that the POC study leaders group is a long established group with regular working meetings. As a result, there are no perceived barriers hindering the exchange of views and ideas. In regard to the number of focus groups organised, typically one group is considered insufficient, as the outcome risks being unique to the behaviour of the specific group (Cohen et al., 2002). In the present case, this risk is eliminated by the composition of the focus group. Work is complemented by preliminary discussions held within WP5 and with members of the project’s Steering Committee, which allowed familiarising participants with the topic. The planned continuation of the focus group discussions is expected to increase the depth of analysis.

### 4.3 Organisation of the focus group

According to Krueger (1988) conducting a focus group occurs in three phases: Conceptualisation, Interview (meeting), and analysis and reporting. The following diagram (Figure 34) illustrates the focus group evaluation process as a continuation of the formative evaluation stages. The two are closely interrelated as summative evaluation builds on the work and findings of the formative stage.
Figure 34. The focus group evaluation process

**Conceptualisation** involves the definition of the scope and methods of the focus group, the selection of participants and the preparation of a questionnaire to guide the feedback collection process. Objective of the Focus Group is to assist the evaluation of the KDC Framework addresses with regards to (a) validity and comprehensiveness, (b) applicability and usability and (c) added-value, on the basis of its operationalisation work in the context of the ADVANCE project. As part of the conceptualisation work, **preparatory discussions** were held within WP5 and with members of the project’s Steering Committee, in order to get advice about the audience(s) to be targeted and how to best formulate the validation questions. During this step, the selection of the POC study leaders and the POC study evaluation workgroup (WP5) as the main target group was made. Other groups were dismissed as being less relevant to the scope of the focus group study, or too focused on specific subtopics and unable to provide high-level insight. An outline of the process including a proposed questioning route was first discussed during a brainstorming session and produced and released for comments before the event. A set of **discussion points** was developed focusing on the collection of information that directly relates to the study’s objectives. The topics were conversational and intended to be easy for the participants to understand. The operationalisation of the KDC Framework in the context of the ADVANCE project is intended to generate insights for its validation. Validation is aimed at establishing the fitness or worth of the KDC Framework for its operational mission. For this reason, during the development of the questionnaire **emphasis was placed on practice rather than on the underlying theory**: on discussing the validity of the tools and instruments...
Chapter 5: The ADVANCE case study

developed to operationalise and materialise the Framework in the context of POC experimentations, rather than on elaborating on abstract conceptualisations. The questionnaire was composed of a set of six broad statements (topics) addressing the three pre-defined evaluation dimensions of the KDC Framework (Table 45). In addition, for each topic indicative open-ended questions were included to encourage exploration of each topic (probing questions), but without offering a view or judgement. Participants were asked to provide their ideas, comments and recommendations regarding the topics. The questionnaire is listed in Appendix 4.

Table 45. Focus Group validation criteria

<table>
<thead>
<tr>
<th>Validation criteria</th>
<th>Discussion items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applicability and usability</td>
<td><strong>Point 1:</strong> This methodology can be followed easily and intuitively</td>
</tr>
<tr>
<td>Comprehensiveness, accuracy</td>
<td><strong>Point 2:</strong> The Framework captures and represents in concrete dimensions the structural and temporal relations among the underlying socio-technical elements of the investigation system</td>
</tr>
<tr>
<td>Applicability, usability and acceptability</td>
<td><strong>Point 3:</strong> The Framework can be used as a basis for planning and implementing vaccine B/R studies</td>
</tr>
<tr>
<td>Added-value, efficiency, and effectiveness</td>
<td><strong>Point 4:</strong> The Framework allows in depth investigation of vaccine B/R studies from different perspectives and at different levels of analysis</td>
</tr>
<tr>
<td>Generalisability and transferability</td>
<td><strong>Point 5:</strong> The Framework can describe any vaccine B/R study</td>
</tr>
<tr>
<td>Innovation</td>
<td><strong>Point 6:</strong> The Framework can serve the purposes of continual analysis, to improve/manage change in established vaccine B/R studies and can also serve the purposes of innovation, to help explore and assimilate emerging technology and scientific advances</td>
</tr>
</tbody>
</table>

In the context of the Focus Group meeting the term **Framework** has been used to denote the proposed instruments and methods for the instantiation of POC studies, namely the Process Map and the Process Planning Canvas. The Process map (and workflow) describes the processes from scoping to protocol approval (scoping, protocol writing, data sourcing, data extraction, data transformation, analysis, archiving and reporting including additional process which was added for output evaluation and compliance assessment) - covering all the performance indicators listed in ADVANCE evaluation framework, supports the formulation and interpretation of the recommendations, and ultimately strengthens the WP5 proposal for the research process map to progress forward into the ‘ADVANCE blueprint’. The process planning canvas is a planning instrument to be used for each stage of the study to align requirements, capabilities and
resources. This Framework represents the operationalisation of the KDC Framework for the instantiation, management and sustainance of POC studies.

The selected focus group method is **Round Robin Reporting**, although not applied in a strict form. This technique is based on specific questions, themes or issues, which the facilitator identifies and shares with the group, and then asks each person to give their reactions and ideas in relation to this topic. Typically, the round robin technique makes sure that each group member to share equally in the group process. In the present case brainstorming was also encouraged to provide additional insight on specific aspects and/or make further suggestions. While not specifically solicited during the Focus Group meeting, the adopted questioning route also combines elements of the **Critical Incident Technique**, in which participants are asked to provide past events as examples while answering questions. In this case, the focus of the discussions is on previous incidents related to the topic rather than speculations and generalisations. In the present case, the experts shared their opinions and insights about future POC study organisation, based on and evoking both the experience of POC1 and the ongoing discussions regarding the forthcoming development of the POC2 study. At the onset of the meeting an introduction to the scope of the meeting, was followed by a brief presentation of the two instruments (Process Map and the Process Planning Canvas) and the underlying principles and concepts. The importance of examining POC studies as a **life-cycle spanning two dimensions (information management and collaboration)** was stressed. Following the key findings of the focus group meeting are presented.

### 5. Results

There was general consensus amongst participants as far as the usefulness of the proposed methodology within ADVANCE is concerned. Table 46 summarises the key information shared during the discussion.

<table>
<thead>
<tr>
<th>Validation criteria</th>
<th>Discussion items</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applicability and usability</td>
<td>Point 1: This methodology can be followed easily and intuitively</td>
<td>The ADVANCE reference process map is easy to comprehend with schematic representations that employ easy to follow annotations (e.g. colour coding that reflects specific points of view).</td>
</tr>
<tr>
<td>Validation criteria</td>
<td>Discussion items</td>
<td>Remarks</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Comprehensiveness, accuracy</td>
<td><strong>Point 2</strong>: The Framework captures and represents in concrete dimensions the</td>
<td>The ADVANCE reference process map can help put the life-cycle of a POC study into perspective. No significant omissions or lacks were identified, with regards to the comprehensiveness of concepts and analysis dimensions and the level of detail of the proposed instruments.</td>
</tr>
<tr>
<td></td>
<td>structural and temporal relations among the underlying socio-technical elements of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>the investigation system</td>
<td></td>
</tr>
<tr>
<td>Applicability, usability and</td>
<td><strong>Point 3</strong>: The Framework can be used as a basis for planning and implementing</td>
<td>The ADVANCE reference process map can fit the purposes of the POC2 study. The methodology will significantly reduce the time needed for the implementation of POC2 and increase efficiency. The ADVANCE reference process map can help plan the new POC study and allow for better overview during its implementation, with all stages and steps of the process identified and explicitly defined.</td>
</tr>
<tr>
<td>acceptability</td>
<td>vaccine B/R studies</td>
<td></td>
</tr>
<tr>
<td>Added-value, efficiency,</td>
<td><strong>Point 4</strong>: The Framework allows in depth investigation of vaccine B/R studies</td>
<td>The ADVANCE reference process map can help - examine the feasibility of protocol development, identifying areas that require particular attention and anticipating potential barriers; - identify bottlenecks and delays in the process.</td>
</tr>
<tr>
<td>and effectiveness</td>
<td>from different perspectives and at different levels of analysis</td>
<td></td>
</tr>
<tr>
<td>Generalisability and</td>
<td><strong>Point 5</strong>: The Framework can describe any vaccine B/R study</td>
<td>The ADVANCE reference process map is not directly tied to specific study cases, technologies or concrete implementation details. The ADVANCE reference process map can be used to adapt the POC1 study protocol for the purposes of the second POC study.</td>
</tr>
<tr>
<td>transferability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Innovation</td>
<td><strong>Point 6</strong>: The Framework can serve the purposes of continual analysis, to</td>
<td></td>
</tr>
</tbody>
</table>
Recognising that POC study organisation and implementation is a complex task, particularly when running in real time, participants recognised the potential utility of the proposed approach for putting the life-cycle of a POC study into perspective (Point 2). Participants agreed that the proposed methodology can fit the purposes of the second POC case (POC2 study) currently under discussion in the context of the project’s Steering Committee (Point 3). The tentative plan for POC2 is to extend the study protocol developed for POC1 to perform both retrospective and prospective investigations of the benefits and risks of pertussis vaccines. The composition of the involved work teams (Principal Investigator, statisticians etc) is expected to remain largely unchanged. In this light, experts view that the proposed systematic approach can be used to adapt the POC1 study protocol for the purposes of the second POC study (Point 6). This will significantly reduce the time needed for the implementation of POC2 and increase efficiency (Point 3). Participants noted that the first POC study was subject to significant delays, and that a clear overview of the study process was often missing. During POC1 there was often uncertainty and discussions about what the next steps should be. Experts agreed that this methodology can help examine the feasibility of protocol development, identifying areas that require particular attention and anticipating potential barriers (Point 4). The approach is not directly tied to specific study cases, technologies or concrete implementation details (Point 5).

The proposed approach can help plan the new POC study and allow for better overview during its implementation, with all stages and steps of the process identified and explicitly defined (Point 3). Furthermore, participants estimated that this approach can help identify bottlenecks and delays in the process (Point 4). With regards to the comprehensiveness of concepts and analysis dimensions and the level of detail of the proposed instruments, no omissions or lacks were identified (Point 2). The methodology itself is easy to comprehend (Point 1), with schematic representations that employ easy to follow annotations (e.g. colour coding that reflects specific points of view). The findings of the Focus Group meeting are supported by the results of the POC1 evaluation (need for transparency etc.) and also by the feedback collected during workshops (Barcelona, London) and working meetings.

Aim of the ADVANCE process map (and workflow) is to provide a comprehensive overview of the top level process of vaccine benefit/risk study implementation, and to facilitate its operationalisation through the identification and mapping of relevant capabilities. In this light the reference model brings together and incorporates several tools and processes already defined.
by the ADVANCE project: Good practice guidelines, Code of Conduct and Collaboration, Ethics and Privacy, and data protection) to feed into the overall ADVANCE research process. The generic process map is intended to facilitate the investigation of POC studies from different perspectives and at different levels of analysis. The reference model describes the process from study inception to protocol approval and execution, also including performance indicators, to allow for performance analysis and the formulation and interpretation of recommendations. Therefore the process map is closely interrelated with POC study evaluation.

As the focus group meeting examined a high-level abstraction of the KDC Framework operationalisation instruments, a follow-up meeting was scheduled to further discuss the adaptation and/or enhancement of the proposed instruments for the purposes of the second POC study. The questionnaire was sent out to all focus group participants as per email. Participants agreed to provide additional feedback prior to the follow-up working meeting. The follow-up focus group meeting with the participation of POC study leaders was organised on March 8.

WP5 has already put forth a proposal for the research process map to progress forward into the “ADVANCE blueprint” or model for benefit-risk assessment of vaccines in Europe. This blueprint or framework will comprise methods, data sources and procedures to rapidly deliver robust quantitative data for the assessment of the benefits and risks of vaccines that are on the market.

6. Triangulation of results

The KDC Framework was examined against individual cases drawn from the work of relevant state-of-the-art research initiatives, IMI PROTECT and WEB-RADR. The IMI-PROTECT project (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium, http://www.imi-protect.eu/) aims to strengthen the monitoring of the benefit-risk of medicines in Europe by developing a set of innovative tools and methods that will enhance the early detection and assessment of adverse drug reactions from different data sources, and enable the integration and presentation of data on benefits and risks. Similarly to ADVANCE, the IMI PROTECT can be regarded as a cohort of case studies. The WEB-RADR project (Recognising Adverse Drug Reaction) aims to detect new drug side effects by mining publicly available web and social media content. The investigation examined the transferability of the KDC Framework in the area of work of the MI PROTECT and WEB-RADR projects, in search of drug safety investigations that cannot be described and assessed with the KDC Framework. The WEB-
RADR scenario was of particular interest to this research, since it represents a case where the data originator (patient, physician) is directly involved in the study process, creating additional requirements with regards to the required socio-technical capabilities. The search for discrepant evidence and negative cases (i.e. real-life investigation scenarios that cannot be described or whose scope cannot be supported by the Framework) yielded no results. Overall, the KDC Framework is generic and comprehensive enough to handle the investigation scenarios proposed by the two projects.

7. Discussion
The ADVANCE case was originally intended as an explanatory case study, facilitating the validation of the developed concepts and structures using new empirical data. However, given the extended immersion in the project work and the operationalisation of the KDC Framework in the form of practical instruments targeting critical aspects of POC study implementation, validation in the context of vaccine safety assumed a formative character, namely, serving not solely to test a theory, but also to refine, improve, and extend it. Guion et al. (2011) explain that research validity refers to whether the research findings accurately reflect the situation and are supported by the evidence. Early in the validation process, the analysis of work documents, reports, deliverables and other outputs of the project provided a first indication of the KDC Framework’s fitment, relevance and applicability to vaccine benefit/risk investigations. Matched against the specificities of a concrete yet generic empirical case the validity of the Framework’s founding principles and the comprehensiveness of its concepts and their interrelationships was initially confirmed. This conclusion was further supported by collaborative work within ADVANCE. While approaching the problem from a domain-specific rather than a systems perspective, ADVANCE’s contribution to the research work was vital as the exchanges within the ADVANCE expert knowledge network amplified the knowledge underlying the KDC Framework and helped crystallise and operationalise it in the form of practical instruments. Empirical validation demonstrated that the present work responds to the need for better alignment of capabilities and resources, improved collaboration, transparency, and more rigorous management over the POC process.
Two instruments were developed on the basis of the operationalisation of the KDC Framework and evaluated in the context of ADVANCE: the ADVANCE generic reference model and the
ADVANCE POC study Evaluation Framework, each drawing from a different area of the KDC Framework (Figure 25). The two instruments are geared towards supporting the instantiation and the evaluation of POC studies respectively. While the applicability and practical value of both instruments has been demonstrated, it has also become evident that the combined utilisation of the two can provide a comprehensive overview of the top level processes of vaccine benefit/risk study and can support design, implementation, sustainance and optimisation, namely all the valorisation models in pharmacovigilance innovation identified (Table 19).
Chapter 6: Conclusions and suggestions for future work

"It is not the strongest of the species that survive, or the most intelligent, but the ones most responsive to change."

Charles Darwin

1. Reflection on the research work

Issues related to drug safety have attracted enormous attention over recent decades. Pharmacovigilance refers to the detection, assessment, understanding and prevention of adverse effects of medicines. At present, pharmacovigilance is experiencing a paradigm shift. The increasing scale of datafication combined with the growing knowledge elicitation capabilities of key technology innovations, present pharmacovigilance with enormous opportunities to improve its effectiveness and widen its scope. Pharmacovigilance is expanding its evidence base and methods beyond traditional approaches (spontaneous report systems, longitudinal data etc) towards sophisticated methods that can identify possible safety signals from real-world evidence and big data. The way forward is the facilitation of knowledge exchange infrastructures that integrate real-world evidence to improve work patterns, processes, and efficiencies across the safety monitoring value chain. New technologies and innovations now under development both within and outside the field of drug safety represent powerful instruments of change. Effective pharmacovigilance innovation requires interplay between research and practice. This research attempted to demonstrate that despite intense investigations into pharmacovigilance processes, gaps remain in the field of research translation strategies. The principal challenge identified is that, although technology is advancing at a rapid pace and accelerating change in every industry, the adoption of innovation for medicines safety monitoring is rather slow. Life-sciences and healthcare are among the most conservative industries, bound by strict regulation. There is a gap between value discovery and value realisation. Innovations initiated within the sector remain long in a tentative state, being considered experimental or auxiliary. Innovation spillovers from other domains are approached with scepticism. Challenges go beyond technical feasibility, to also include questions of rapid access to “traditional” data sources and of effective exploitation.
of emerging data sources, governance and coordination issues, heterogeneity in the scientific and organisational focus and interest of the involved entities etc. Nonetheless, in the digital age all industries will eventually be transformed. With change being a continuous process, for pharmacovigilance this represents its own era of “Digital Darwinism”, during which new directions are opening fast and new challenges emerge, as to how the sector adapts in order to draw benefit. To harness the potential of innovation, address challenges and mitigate the risks inherent in the massive technological changes the sector must develop a new information-driven knowledge creation processes for the digital world. As technology advances, new sources of evidence and new investigation methods emerge, creating new knowledge discovery opportunities. Despite the potential of these methods and their growing capabilities as they move towards a maturity level, there is always a trade-off between the potential benefits and the limitations associated with their use, which needs to be considered in the design of real-life vigilance systems. This is the reason why formal pharmacovigilance schemes appear hesitant or slow in the adoption of cutting-edge innovations, although they acknowledge that technology can help explore different types of medical information to uncover the traces of new knowledge not readily apparent in formal approaches.

Several key uncertainties were identified when examining the current state, with regards to the effective valorisation of knowledge sources (Chapter 1.2). The answer to these questions is not simple and a distinction needs to be made between the actual value that can be achieved in real-world situations and the theoretical capabilities of technologies. In the pharmacovigilance sector innovation is acceptable only when the controlled and proven use of new technology can be ensured. This is because, although technology and scientific innovations represent an essential driver for medicines safety investigations, in real-world situations usable (actable) knowledge can only be generated when innovation meets certain preconditions and compliance criteria. The present inquiry concluded that while the investigation process is inherently knowledge intensive, and can benefit considerably from the application of rigorous, state-of-the-art scientific methods and novel technologies for evidence elicitation, relevance to the actual application context needs to be ensured, in order to achieve value. An in-depth investigation of the socio-technical ramifications of knowledge discovery is imperative, in order to develop effective work processes for knowledge extraction in real-life situations. Furthermore, a new paradigm for the conceptualisation of the space, in which knowledge discovery takes place, is called for. An
ecosystem-based view of the sector can provide a solid basis for the analysis of the emerging information value-chains and the resulting strategic partnerships and collaborations. In the light of the above, the present research investigated and proposes a new paradigm for collaborative, information-driven pharmacovigilance. Conceptualised in the form of a comprehensive Reference Framework for medicines safety innovation (the Knowledge Discovery Cube (KDC) Framework), aim of this work was to (a) deepen the collective understanding of how a principled, collaborative and balanced pharma safety data ecosystem can be organised, (b) guide and educate stakeholders towards the optimisation of these services and (c) provide useful reference points for the ongoing research and development process in the field. The principle function of the proposed Reference Framework is to align and coordinate the broad set of capabilities needed for setting up drug safety investigations and studies that meet particular outcomes. This goes beyond the establishment of technical capability and competence and involves a strong social dimension.

At the core of the developed Knowledge Discovery Cube Framework (Chapter 4.B) stands the cube metaphor (Figure 21), which links together the three building blocks and determinants of the value of a medicines safety investigation (data evidence, methods, socio-technical capabilities). In a given socio-technical context, safety monitoring mechanisms apply relevant investigation methods on available information sources, supported by relevant socio-technical capabilities, in order to achieve value, namely, to generate knowledge and insights for informed decision making. The present research work has established a framework for examining the connections, between the intrinsic characteristics of knowledge items, the capabilities that support and enable the creation of value and the achievement of the investigation goals. It has also produced a vocabulary of concepts for the domain of medicines safety research, proposing concise definitions and detailed descriptions of the respective constructs and their interrelationships.

However, the KDC Framework is not intended as a static model of the domain. The KDC Framework considers Research Investigations as being constantly in a state of “imperfect development”, with evaluation and foresight shaping the ground for continual improvement and innovation. Aim of the KDC methodology is to be instrumental to the process of innovation, allowing for a continuous interpretation, reinterpretation and alignment of the past, present and future of pharmacovigilance (Table 11). As highlighted by Kaplan & Orlikowski (2014), new
visions of the future trigger reconsiderations of current concerns, as future projections are intimately tied to interpretations of the past and the present. Through its Research Investigation life-cycle model, the KDC Framework delineates causal and explanatory relationships in “what is” and establishes practical references to facilitate the instantiation of investigations and the valorisation and assimilation of emerging domain knowledge and innovation for developing “what could be” (optimisation, innovation through translation of research into practice).

However, this is not a one-way process moving from technology innovation to drug safety innovations, but a reciprocal process of interaction and exchange, with needs and requirements collected and lessons learned from practice influencing research and development (R&D strategic planning).

At the basis of the KDC Framework stands the ecosystem paradigm of collaborative knowledge creation. The KDC Framework approaches medicines safety investigations as a collaborative learning exercise, viewing research investigations as cross-disciplinary co-operations that involve a diversity of partners who engage in mutual learning and jointly develop cooperative activities, combining their operational and organisational strengths to advance pharmacovigilance. Beyond the design and implementation of RIs, the KDC Framework is intended to facilitate partnership building for knowledge creation and promoting joint innovation, including bottom-up innovation. In this light an important task in the operationalisation of the KDC Framework is the identification of Collaboration Impact Zones, i.e. those junctures where interactions and the exchange of expertise and information take place, and accommodate their operational and organisational requirements for the development of common spaces for collaborative knowledge creation.

The socio-technical spaces built around RIs, in which the discovery of new knowledge takes place re envisaged as digital knowledge discovery “laboratories” for evidence elicitation. The aim of these “Smart Investigation Environments” (i.e. the socio-technical systems representing the instantiation of RIs), is to provide the best evidence at the right time to support collaboration and decision-making regarding the safety of licensed medicinal products. Research investigations can be combinatorial, exploratory or transformational, supported by simple, complicated or complex research designs. In line with the conceptualisation of RIs as evolving and “maturing” processes, the Smart Investigation Environment of a given RI is adaptive and evolving, collaborative and encompassing.
2. The research path

The overarching aim of this research, as stipulated at the onset of the present inquiry, was to explore the emerging landscape in pharmacovigilance and to develop a Reference Framework for collaborative, information-driven innovation in the field of pharmacovigilance that can be used to describe and assess the implementation of medicines safety investigations, as well as to guide and educate stakeholders towards the design, optimisation and innovation of pharmacovigilance implementations. In terms of the initial objectives, the present research successfully accomplished its goals, as stipulated in Chapters 1 & 3, with regards to the exploration of the domain (Chapter 2), the analysis and development of the KDC Framework (Chapter 4), and its evaluation and empirical validation in the context of vaccine pharmacovigilance (Chapter 5). As intended, the current state and emerging directions in the field of pharmacovigilance were meticulously studied and analysed from multiple perspectives to generate working hypotheses (high level and refined requirements) for the Reference Framework. The developed KDC Framework was validated empirically in the context of the ADVANCE case study.

A variety of sources informed the research work on its way from developing an in-depth understanding of the emerging evidence landscape in pharmacovigilance and the needs of the sector (benefit/risk analysis, real-time safety monitoring, studies of effectiveness, etc.), to exploring relevant models and theories in the field and beyond and defining concepts and paradigms of relevance, to establishing the founding principles of a Reference Framework, to developing the Framework and validating it in theory and in practice.

The adopted research approach could be described as a combined empirically based (inductive) and theory-informed (deductive) endeavour, which constantly iterates between theory and observation. It consists of inductive discovery (induction) and deductive proofing (deduction), building on case study analysis. It builds on the principles of triangulation, multi-methodological approach, and ongoing and iterative investigation. The research methodology adopted for the present research work is grounded on empirical data and theory, to ensure that the developed Framework is theoretically robust and pragmatic, flexible and comprehensive. Observation and theory are the two pillars of the present research, which operates interchangeably at two levels: a theoretical level and an empirical level. Induction was employed as part of theory-building, in order to infer theoretical concepts and patterns from observed data. The process is incremental, synthesising cross-case and cross-sector evidence, to allow for a new
understanding of the status and prospects of the research area. Deductive work revolved around theory-testing, the validation of concepts and patterns known from developed theory using new empirical data. It should be stressed that theory-testing was employed in a formative way, namely not solely to test a theory, but also to refine, improve, and extend it. The resulting deliberations draw from relevant theories and the findings and conclusions of scholarly research, guidelines, policy documents and reports, and other resources from within and outside the field of health and life sciences. With regards to empirical data, research was based on the concept of viewpoints (Kotonya & Sommeiville, 1996) for the identification of important aspects, specific to the pharmacovigilance domain. The aim was to develop an understanding of the pharmacovigilance ecosystem, its requirements and constraints and also its dynamics. The identification of direct stakeholder perspectives, coupled with indirect viewpoints (broader organisational, legal etc requirements and concerns that need to be taken into account) was deemed imperative. Technology foresight represents an important dimension in this analysis. In addition to an investigation of the current and the emerging landscape of drug safety, some of the overarching challenges that condition its structure and operations were investigated from a number of viewpoints. The perspectives explored include Technology (technology foresight), Information (knowledge value chains), Collaboration structures (pharmacovigilance ecosystem), People (ergonomics) and Ethics (Ethical & legal considerations).

Aim of forward looking in the present context was to explore methodological requirements to facilitate the development of capabilities for harnessing technology innovation, and to set priorities for innovation activities in pharmacovigilance methods. Particular emphasis was placed on trends analysis of critical emerging technologies, i.e. technologies that have a strong potential to influence the public health and life sciences sectors and help create efficiencies along the entire safety-monitoring continuum. The research identified and analysed several disruptive technologies that are expected to transform the sector (big data & data analytics, mobile Internet, automation of knowledge work, the Internet of Things, cloud technology etc). The aim was to identify the driving forces of today’s technical innovation and plan for long-term success in the field of pharmacovigilance. Data was subsequently consolidated in the form of high level insights, on the basis of which a search for relevant or similar domains and theories was launched in order to inform the Framework development process. Design knowledge was also
explored, specifically targeting relevant system design paradigms. On this basis refined requirements were formulated.

A rigorous and comprehensive approach was applied for the evaluation of the research work and the developed KDC Framework. For the purposes of internal validation a retrospective review of the design process and research process are amongst the research methods that were applied to verify that this model satisfies all design requirements. External validation is intended to verify that the objective of the research work is accomplished with respect to the world beyond the research context. Therefore, for the purposes of external validation empirical confirmation was sought through a rigorous and comprehensive approach that addresses three important dimensions: (a) validity and comprehensiveness, (b) applicability and usability and (c) added-value. The process involved (a) an exploratory investigation of the KDC Framework’s ability to describe state-of-the-art drug safety cases taken from innovative research projects and (b) a case study in the field of vaccine pharmacovigilance, including the operationalisation of the Reference Framework for supporting the systematisation of vaccine safety studies.

The first method targeted the first validation dimension (validity and comprehensiveness of the Reference Framework), while the second addressed all three dimensions. Operationalisation in the context of vaccine safety was intended as an explanatory case study that enables the validation of the developed concepts and structures using new empirical data. It should be stressed that validation in the context of vaccine safety was also intended as a formative instrument, namely not just to test a theory, but also to refine, improve, and extend it.

The developed framework was operationalised and validated in the context of vaccine safety assessment and monitoring. The contribution of the ADVANCE project to the present research work was vital as the exchanges within the ADVANCE expert knowledge network amplified the knowledge underlying the KDC Framework and helped crystallise and operationalise it in the form of practical instruments. ADVANCE provided the field for the empirical validation of the KDC Framework. The present research developed a symbiotic bidirectional relationship with the project, following, complementing, and supporting the work of ADVANCE (contributing to the creation of the POC study evaluation framework, the evaluation of the first POC study and assisting the planning and organisation of the subsequent POC investigation with instruments and methods building on the KDC Framework) and learning and being informed by the work and
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outcomes of the project. Feedback regarding the progress and challenges of the project was both formative to the development of the KDC Framework and evaluative.

Early in the validation process, the analysis of work documents, reports, deliverables and other outputs of the project provided a first indication of the KDC Framework's fitment, relevance and applicability to vaccine benefit/risk investigations. Matched against the specificities of a concrete, yet generic, empirical case, the validity of the Framework’s founding principles and the comprehensiveness of of its concepts and their interrelationships was initially confirmed. This conclusion was further supported by collaborative work within ADVANCE.

Despite approaching the problem from a domain-specific rather than a systems perspective, participant observation of the ADVANCE case contribution to the research work was of particular significance. The KDC Framework validation was a spiralling learning process rooted in actions and experiences taking place within an expanding “community of interaction”, as well as in formal feedback. Validation involved both tacit and explicit steps. The former include project meetings, presentations and discussions about the scope, progress and activities of the project. The latter includes work meetings and workshops, revolving around the structuring of the POC study Evaluation Framework and the outcomes of the evaluation work. Qualitative feedback was collected at various points of the project work, with the most significant instances of explicit feedback collection being during the development of the POC Evaluation Framework, the evaluation of the first proof-of-concept study (POC1) organised by the project, and the planning stage for the organisation of the second POC study. In this process, the intended use of the KDC Framework as a strategic planning, instantiation, maintenance and optimisation instrument for drug and vaccine safety studies was validated. Instruments and methods developed according to the KDC Framework and adapted for the planning of the second POC study were validated through dedicated participatory activities (focus group discussions). Instruments and methods for the instantiation of POC studies developed according to the principles and of the KDC Framework (the ADVANCE Process Map and the Process Planning Canvas) were evaluated. Aim of validation was to examine the comprehensiveness and fitment of the KDC Framework, identify potential deviant cases and other shortcomings of the present framework from a pragmatic, implementation-oriented perspective. There was general consensus amongst participants as far as the usefulness of the proposed concepts and methods, while a proposal has already been put forth for the research process map to progress forward into the
“ADVANCE blueprint”, the project’s comprehensive framework, which will comprise methods, data sources and procedures to rapidly deliver robust quantitative data for the assessment of the benefits and risks of vaccines that are on the market.

While recognising the limitations of the analysis, it can be concluded that the present research has largely achieved its original aim and objectives, set out in Chapters 1 (Introduction) and 3 (Methodology).

3. Research Hypotheses revisited

The principal objective of this research work was to develop a **Reference Framework for collaborative, information-driven innovation in the field of pharmacovigilance** that can be used to describe and assess the implementation of medicines safety investigations, as well as to guide and educate stakeholders towards the design, optimisation and innovation of pharmacovigilance implementations. At the onset of the present research work three research objectives (research hypotheses) were identified:

<table>
<thead>
<tr>
<th>Hypothesis 1</th>
<th>Hypothesis 2</th>
<th>Hypothesis 3</th>
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<tr>
<td>The development of a Reference Framework for collaborative, and information-driven pharmacovigilance is feasible</td>
<td>The KDK Framework for collaborative, information-driven pharmacovigilance can deepen the collective understanding of how a principled, collaborative and balanced pharma safety data ecosystem can be organised and guide and educate stakeholders towards the optimisation of these services.</td>
<td>The KDK Framework for collaborative, information-driven pharmacovigilance can serve the purposes of continual analysis, providing a mechanism for shaping research and managing technology adoption in an informed and intentional manner.</td>
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In the case of exploratory research, whose purpose is to develop knowledge and generate hypotheses about the phenomenon under study, the formulation of meaningful research hypotheses is questionable. The present study has a strong exploratory dimension. Consequently, the aforementioned hypotheses mainly denote the purpose of research and the main criteria of its success. All three hypotheses are supported by the present research and its outputs. This was further confirmed through its operationalisation of the KDC Framework in the context of the
ADVANCE project, during which, first the need for and the merits of a systematic approach were acknowledged and subsequently the usefulness and value of the KDC Framework were confirmed. According to the original research design, the reference framework is expected to:

- allow stakeholders to seek and find affordances that need be mobilised in terms of resources, devices and systems by decontextualising the objects of experience, reducing them to their useful properties and determining their interrelationships.
- provide useful reference points for the ongoing research and development process in the field, in terms of both strategic planning and innovation adoption.

The developed Knowledge Discovery Cube Framework fulfils these needs. The present research has achieved its aim to develop a framework that is informed (in terms of its relationship to and knowledge of the application domain) and pragmatic, with an ability to enable learning and action as knowledge evolves. This will allow establishing baseline references to help define, design and implement electronic investigations and research protocols, effectively exploring diverse knowledge sources in alignment with the implementation context.

Against the backdrop of the Medical/Drug data and technology revolution, the Knowledge Discovery Cube Framework represents a method for continual analysis, a mechanism for managing technology adoption in an informed and intentional manner. The aim was for the Reference Framework for drug safety investigations to support the valorisation of innovations in an evolving technological and social landscape. The core mission of the Reference Framework is the digitisation and operationalisation of known methods, the development/discovery of new methods, and the improvement and optimisation of instantiated investigations. In this context three distinct models of innovation valorisation have been identified (Table 19) and accommodated:

- **The protocol model.** Conventional “analog” medicines safety investigation processes are being transformed into “digital” knowledge-driven value chains, by assessing and aligning the scientific protocol with data evidence and required capabilities (combinatorial use of innovation).

- **The problem-solving model.** Additional medicines safety questions are addressed through the design and development of new knowledge discovery practices, grounded on new technologies and new sources of evidence (exploratory use of innovation).
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- **The validation model.** New medicines safety insights are generated by exploring the usefulness and application potential of emerging innovations, leading to the development of new protocols for new questions (transformational use of innovation).

This research work has produced a reference framework and operating model for the effective analysis of drug safety investigations that is flexible and transferable and can support any research investigation.

The fourth Hypothesis (H₄) referring to the generalisability of the KDC Framework is supported by the findings of the theoretical and empirical evaluation, subject to the limitations discussed in Section 4.

4. Limitations

Although the present research has largely reached its objectives, some unavoidable limitations associated with the implementation of the research plan need to be acknowledged.

- **Number of cases studied as part of the case study.** In principle, the exploration of multiple cases (multisite research) has significant advantages over single-case designs, strengthening the results obtained and providing a firmer basis for generalisation. However, the operationalisation and empirical validation of a Reference Framework is a strenuous task, requiring effort, time and resources. Another major barrier is that it is very difficult to get new theoretical approaches accepted and used in practice by market regulators, industry and other relevant bodies. Consequently, while it was a considerable advantage for the present research to be able to perform a detailed study and to collect feedback and draw insights from the ADVANCE case, it would not have been possible to perform the same exercise in other case study sites, in the context of the present work.

- **Sample size and provenance.** The absence of broad community involvement in the validation of the Framework could potentially be regarded as a limitation. The empirical validation of the KDC Framework involved participants of the ADVANCE projects. However, as an international set of experts from all relevant domains was mobilised and engaged long term in the formative and summative validation of the Framework, it can be concluded that the validation community was sufficiently rich in expertise and experience. Furthermore, while additional proof-of-concept case studies are expected to bring refinements and additions to the operationalisation instruments (particularly with regards to...
the evaluation criteria, and the ensuing corrective or other actions) no changes are expected with regards to the overarching KDC Framework.

- **Instruments used for data collection.** Due to time restrictions, and planning constraints within the ADVANCE project, formal activities aimed at the collection of empirical data directly from domain experts were limited to the organisation of focus group meetings. Personal interviews, organised as follow-up actions, would have provided additional insight into the present work. Acknowledging this potential deficiency, and in order to mitigate the associated risks, the present research put particular emphasis on observation and document analysis as a source of valuable in depth knowledge.

In principle, these limitations constitute constraints on the generalisability on the developed reference Framework.

**Other risks and challenges addressed:**
Several limitations inherent in the adopted research methods were acknowledged during the research planning stage and measures were taken to mitigate potential risks to the final outcomes. The principal considerations are outlined below.

- **The research work was qualitative.** To overcome the inherent limitations of qualitative research and increase the internal validity of the research work, the study adopted an incremental approach and incorporated multiple perspectives that served as controls. Triangulation of data was rigorously pursued, collecting information from a diverse range of settings, and using a variety of methods.

- **The role of the investigator.** The researcher is viewed as key instrument of data collection and analysis in qualitative research which is an inherently a reflective process with regards to both its implementation and outcomes (Willis et al., 2007). The research methods, from technique to purpose, can evolve across the research process. The risk of researcher bias is high, as the researcher's position and any personal biases or assumptions may impact the inquiry. Particularly, with regards to research is much more participatory studies (as is the case of the present case study) where the qualitative researcher immerses themselves in the setting, their perceptions and presence can have a profound effect on the subjects of study. In light of this risk, the present research was conducted through constant, critical, and self-
reflexive enquiry about the researcher’s role in the research process (Holloway & Galvin, 2016) (Chapter 3).

- **Lack of prior research studies on the topic.** The topic addressed in the present research is relatively new. There exists no general comprehensive reference framework to guide the investigation, implementation and sustainment of collaborative information-driven medicines safety innovation processes. Related work has focused on developing guidance for protocol development, implementation aspects, or reporting outcomes, but no comprehensive reference framework has been proposed to accommodate the complete life-cycle, with a view to incorporate technology and other innovations and changes and the emerging paradigms of pharmacovigilance. Only recently, (in 2018) other scholars explicitly acknowledged the need for a “transparent and scientific framework for evaluating new data sources and technologies, and measuring their impact on pharmacovigilance process and research relative to the sources and approaches currently used” (Bates et al., 2018). For this reason, and to compensate the lack of prior work, the present inquiry adopted an inductive approach that is grounded in data, informed by theory and validated in practice.

- **The development of the KDC Framework was inductive, grounded on data.** While great care has been applied in identifying areas of relevance to the scope of the KDC Framework, the outcome is inherently limited to the domains included in the original analysis. In theory, this could be restrictive to the scope of the developed Framework and for this reason several measures have been taken to mitigate potential risks (triangulation, theoretical analysis through the identification and analysis of adjuvant theories etc). The emphasis placed on empirical analysis (operationalisation and validation) was also intended to ensure the systematic and explanatory power of the KDC Framework.

- **Limitations of foresight.** Foresight set out to generate visions of pharmacovigilance, by exploring technological developments and relevant social changes, in order to develop an understanding of possible future developments in the field. Nonetheless, the future is not predetermined, and can evolve in different directions than the ones anticipated.

- **Practical assessment.** A major barrier to the empirical validation of holistic frameworks and forward looking methods is that it is very difficult to get new theoretical approaches accepted and used in practice. The ADVANCE project, being a research initiative itself, but grounded on real-life practice and representing all the key stakeholders in the field, provided a valuable
space for the empirical validation of the KDC Framework. The use of case study-based validation (POC1 and POC2 studies) provided detailed contextual analysis for the refinement and evaluation of the Framework. However, case study is often disputed as a tool, with regards to whether generalisations and “lessons” can be derived from a specific case (case selection criteria, data collection methods, etc). While providing realism to the investigation, a case study represents a narrow field of study, whose results often cannot be extrapolated to a generic hypothesis. To prevent this risk, the relevance and suitability of the ADVANCE cases for the purposes of the present research were carefully examined. The suitability of ADVANCE was confirmed by our preliminary analysis. POC studies within ADVANCE represent “experimentations”, usable for the generalisation of the ADVANCE system. The criteria of representativeness underpinning the selection of POC cases by the project, make the ADVANCE vaccine studies representative of a large cohort of studies (vaccine benefit/risk studies) and thus suitable for the present research as well. With regards to risks associated with the case study implementation, the validation methodology set a clear rationale for the ADVANCE case study identifying the phenomena of interest and the appropriate field methods, defining concrete research questions (validation dimensions) and data collection methods.

- **Degree of development of POC studies.** The fact that the ADVANCE project was still at an early stage of development at the time of this research, could be considered as a limitation, particularly, since typically more valuable conclusions can be reached at the end of the project work. The workplan of the project imposed some restrictions to the timeplan of the present research. Nonetheless, the fact that the project was still at an early stage of development was beneficial to the present research, since it allowed for long term observation and immersion to the project activities, thus providing an inside view of vaccine pharmacovigilance innovation. The operationalisation of the KDC Framework in the context of ADVANCE allowed for the testing of the principles and capabilities of the KDC Framework against concrete, real-life work processes and issues. This would not have been possible, were the project nearing its completion. Future results are expected to populate the developed instruments with concrete indicators and benchmarks to turn the vaccine safety instance of the KDC Framework into a production pipeline.
Focus on vaccine pharmacovigilance. The initial scope of the reference framework is broader, targeting medicines safety and pharmacovigilance at large. The selection of the subdomain of vaccine safety for its validation is a potential limitation to its applicability. To this argument it should be noted that vaccine and medicines vigilance have many commonalities. In addition, the analysis methods employed during the design phase are set to guarantee the fitment of the KDC Framework for medicines safety investigations. This was also confirmed through a theoretical comparison of the Framework against generic investigation cases from other state-of-the-art research projects.

5. Contributions to research and practice
The KDC Framework bears key implications for both research and practice.

5.1 Theoretical contribution
In addition to practical implications, the present research contributed to theory by introducing the topics of Knowledge Translation and Research Translation in the pharmacovigilance domain. In this line, it further contributed to existing prior theory by extending, applying, and validating a theoretical model for Knowledge Translation for the purposes of pharmacovigilance innovation. From the analysis, it became evident that a global Knowledge Translation model is more aligned with the needs of pharmacovigilance. Several models and approaches were investigated. The developed KDC Framework brought together elements of several frameworks to extend the CIHR model, with the addition of the analysis dimension it was lacking. The CIHR model provides a good overview of the research translation landscape, but lacks the sophistication and granularity required to accommodate the specific requirements of the pharmacovigilance domain, particularly with regards to research utilisation. Learnings from other Knowledge Translation models, which partially address the requirements, and from other relevant domains were incorporated to address the multidimensional and complex nature of pharmacovigilance. The model has been extended for the purposes of pharmacovigilance, with the introduction of the concept of maturity (imperfect design), the notions of attainable and achieved benefit, the innovation points, the combined examination of people, goals/tasks, structure and technology etc. The resulting Framework can support the design, implementation, sustainance and optimisation of pharmacovigilance innovations is a reflective, iterative, interdisciplinary and participatory process that links knowledge (science) and action (practice), by combining,
refining, interpreting and communicating knowledge within a socio-technical system. The present research studied extensively the emerging landscape in pharmacovigilance, developing a taxonomy of new data evidence utilisation cases (Table 27) in the context of pharmacovigilance and a taxonomy of innovation valorisation models (Table 19).

5.2 Contribution to practice

Against a background of rapid technological progress, the pharmacovigilance sector is in a process of reinventing itself, moving from analog to knowledge-driven digital processes. In this process researchers need to jointly consider and combine ideas and affordances from information systems and data science with life sciences, epidemiology and healthcare. The principal contribution of the developed Reference Framework is that it allows for the systematisation of knowledge in the drug/vaccine safety domain, bridging the two traditionally disjoined domains of information systems and life sciences and integrating formerly separate parts of knowledge. The principal contribution to practice is that the KDC Framework allows to advance implementation of Research Investigations in practice by providing a consistent taxonomy, terminology, and definitions on which a knowledge base of findings across multiple contexts can be built. To harness the potential of innovations, and discover new opportunities the constant interplay between unsolved problems and ideas and new or emerging technologies is required. The KDC Framework serves as a bridge between research and practice that allows for the valorisation of emerging innovations, by providing a control context for the development and testing of hypotheses regarding the applicability and practical value potential of emerging innovations, taking into consideration key factors from the macro environment. Reversely, the KDC Framework allows deriving recommendation for research, i.e. the identification and prioritisation of technology areas, in which targeted research is required in order to advance the state of pharmacovigilance. The KDC Framework can be used proactively, to guide research both within the pharmacovigilance sector (allowing for paths in potenia to be explored, pointing out fruitful problems etc) and outside drug safety but aligned with and aimed to advance the sector (proposing totally new lines of research to benefit pharmacovigilance).

The KDC Framework acts as an effective coordination mechanism for the design, instantiation, improvement, maturity and systematisation of Research Investigations. Through a pragmatic evaluation of contextual factors, the KDC Framework allows for, feasibility assessment and alignment to ensure the value and promote the maturity of the investigation moving from theory.
to instantiation towards becoming established practise. RIs needs to be continuously tested and improved in the light of changes in the wider context in which they are instantiated and operated. In this process, the KDC Framework is both generalising and explaining lower abstraction level knowledge and can thus promote theory development and verification about what works where and why across multiple contexts and on various levels of analysis. Key indicators are used to facilitate continuous quality improvement. Stakeholders can adapt the KDC Framework to their specific needs, selecting the context that is most relevant for their particular study setting, describe the framework’s constructs accordingly and use this to guide diagnostic assessments of implementation context, evaluate implementation progress, and help explain findings in research studies or quality improvement initiatives. For example, focusing on different stages of the RI life-cycle, methods, data evidence and capabilities can be viewed from various angles (Figure 35):

![Figure 35. Analysis perspectives facilitated by the KDC Framework](image)

The KDC Framework empowers pharmacovigilance stakeholders to set strategic directions, to ask “the right questions” about critical aspects and guides users’ thinking and understanding towards practical solutions. Analysis can be conducted on a macro- (high level investigation of the drug safety system), meso- (from the perspective of Intermediary Organisations/National Authorities) or micro-level (from the perspective of data originators, patient & healthcare practitioners) (Figure 36).
The KDC Framework is intended as a dynamic valorisation cycle, a continuous knowledge creation process, allowing for timely updating, so as to facilitate and support collaborative strategic planning and coordination around drug/vaccine safety. As such it will be able to reflect emerging reality, current practice, and strategic goals, to respond and adapt to changing circumstances and needs, enabling stakeholders to derive concrete actions needed when striving for the desired improvements.

While the approach promotes digitisation, the proposed methods are not aimed at sidelining experts. Instead, the aim is to make involved experts more knowledgeable of the implications of the investigation process, to make them aware of the pre- and post-conditions of individual process stages and to help them make informed decisions throughout the process.

The contributions of the present research span several levels:

- Application level (pharmaceutical industry, SMEs/Organisations, National Authorities);
- Research level (ICT/Creative tools providers and innovators, academics and researchers, ICT companies); and
- Public policy level (Policy makers, legislators, regulators).

Stakeholder groups directly involved in or external to the Pharmacovigilance ecosystem are expected to make different use of the KDC Framework:
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Table 48. Main target group of the KDC Framework

<table>
<thead>
<tr>
<th>Target Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacovigilance ecosystem</td>
<td>The focus of the KDC Framework is on practice, research and innovation. The process has been predominately about synthesising the knowledge in the wider stakeholder community and bringing it together in a structured form to facilitate operational improvements and future strategic planning. It allows stakeholders have a better insight on the future capabilities of technologies, including apparent trends they could potentially exploit.</td>
</tr>
<tr>
<td>R&amp;D (Academia and Research)</td>
<td>Rather than speculating about the future requirements of the pharmaceutical industries (about the tools, applications and services that will be of service in the future), through this Framework they can identify which areas are suitable for additional research and development work, i.e. technologies and tools that are desired for the future but are not strongly supported at present.</td>
</tr>
<tr>
<td>Legislators and Policy makers</td>
<td>To identify critical gaps that require intervention. Policy makers can use the Framework to steer future policy making</td>
</tr>
</tbody>
</table>

The effects of the KDC Framework as a valorisation instrument for technological innovations can be instrumental to pharmacovigilance on both an application and a theoretical level. On the application level it can be applied for influencing the operations and practices, the efficiency and effectiveness of pharmacovigilance methods. On a theoretical level it can serve for guiding the ideation, design, instantiation and systematisation of new pharmacovigilance practices. Value can be achieved on several dimensions: (a) Quality: better decision making, improved patient safety; (b) Operational agility: accelerated rate of innovation, flexible capacity deployment; (c) Speed: reduction in cycle times, accelerated instantiation timelines, rapid conceptualisation and planning; etc. Intangible benefits include partnership building, changing behaviour and stimulating spill-over effects.

Specific contributions include the development of practical instruments for benefit/risk study instantiation, and management, and for the evaluation of vaccine benefit/risk studies. Two instruments were developed on the basis of the KDC Framework: the ADVANCE generic reference model for the instantiation of POC studies (comprising the ADVANCE reference process map and the process planning canvas) (Chapter 5.B) and the ADVANCE POC study Evaluation Framework (Chapter 5.C), each drawing from a different area of the KDC Framework.
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6. Impact

The KDC Framework captures and represents in portrayable dimensions the structural and temporal relations among the underlying socio-technical elements of the investigation system. The Reference Framework can help stakeholders put existing guidance in context. The Framework relies on and does not overlook existing guidelines, recommendations and standards. The methodology is intended to be instrumental. It establishes a basis for examining the connections, between the intrinsic characteristics of knowledge items, the available capabilities and the achievement of various investigation goals. It represents a fundamental starting point to guide deliberation and action based on relevant guidance. On the basis of the KDC Framework, several aspects pertaining to the lifecycle of an investigation can be planned, managed and controlled in a systematic way. The reference framework can provide: (a) a common language among all involved stakeholders; (b) epistemological and methodological grounding within appropriate theories and guidelines; (c) guiding points against which pragmatic decisions can be made; (d) practical directions to the design and development of investigations; (e) a structure for the organisation of collaborations; and (f) a structured approach to managing required capacities in order to deliver on objectives. In this manner, it enables the design, implementation, sustainance and optimisation of pharmacovigilance innovations is a reflective, iterative, interdisciplinary and participatory process that links knowledge (science) and action (practice), by combining, refining, interpreting and communicating knowledge within a socio-technical system. The application of the Knowledge Discovery Cube Framework allows establishing baseline references: concrete guidelines, benchmarks and reusable artifacts (e.g. investigation protocols) for the effective implementation of any Evidence Creation Process. Combined with a broader investigation of health/drug information sources and methods, the KDC Framework can assist the systematisation and scaling of the evidence creation process, methods and systems in the future to improve knowledge and decision making throughout the life cycle of the vaccines and drugs in general.

7. Future work

Further research will concentrate on affirming the results and on identifying further strategies for their operationalisation. An important area for future research is the replication of the study in other pharmacovigilance settings. Overall, an empirical investigation of the research questions
and development and testing of research hypotheses on a broader scale should better assess the identified challenges. The present research has identified and evaluated the core features of the Reference Framework. Further investigation will provide detailed information about the requirements of different pharmacovigilance settings to enable the development of a taxonomy of required and recommended features.

Future work should be geared towards the definition of a Capability Maturity Model for RQs (RQ-CMM model) to assess specific RQ implementations against a scale of predefined maturity levels. The development of a requirements checklist for the RQ-CMM is also recommended: a Capability Maturity scoreboard for balancing the required Technologies (Tools), Methods (Processes), Organisational & regulatory aspects and Actors based on the available Knowledge Resources standardisation of domain knowledge, concepts and methods on the basis of the Framework. The framework would thus serve as an assessment grid for RQ investigations, mapping and investigating RQ requirements against engineering and organisational characteristics (capabilities) and yielding recommendations that could span several dimensions that refer to different activity areas and/or stakeholder groups.

"It is not the strongest of the species that survive, or the most intelligent, but the ones most responsive to change."

Charles Darwin
Appendix 1

Vaccine pharmacovigilance

The WHO (2017a) defines vaccine as “a biological preparation that improves immunity to a particular disease”. There are different types of vaccines (Milligan & Barrett, 2015). A vaccine typically contains an agent that resembles a disease-causing microorganism, and is often made from weakened or killed forms of the microbe, its toxins or one of its surface proteins. This agent stimulates a person’s immune system to recognise the agent as foreign, destroy it, and "remember" it, so that the immune system can more easily recognise and destroy any of these microorganisms that it later encounters. Vaccines can be prophylactic (example: to prevent or ameliorate the effects of a future infection by any natural or "wild" pathogen), or therapeutic (e.g., vaccines against cancer are being investigated). Prophylactic vaccines can have a broad impact on health as they have the potential for far-reaching effects (Doherty et al., 2016).

Vaccines produce immunity to a specific disease, subsequently protecting the person from that disease. The process by which a person becomes protected against a disease through vaccination is called immunisation. While no vaccine is 100% effective, the evidence demonstrating the benefits of immunisation are significant: when used broadly in communities, several vaccine preventable diseases could be controlled and some may be eliminated (Roush et al., 2007; Andre et al., 2008; Okwo-Bele & Cherian, 2011; Council of the European Union, 2011).

Vaccination is regarded as one of the most effective interventions to prevent life threatening communicable diseases and is estimated to avert an estimated 2.5 million deaths each year (WHO, 2013). In the last decade, great advances have been made in developing and introducing new vaccines and expanding the reach of immunisation programmes significantly lowering the prevalence of many infectious diseases (Levine et al., 2011; WHO, 2013). As a result of immunisation combined with other health care and development Interventions, the annual number of deaths among children under five years of age fell from an estimated 9.6 million in 2000 to 7.6 million in 2010, despite an increase in the number of children born each year. The WHO (2013) notes that this century promises to be the century of vaccines, with the potential to eradicate, eliminate or control a number of serious, life-threatening or debilitating infectious diseases, and with immunisation at the core of preventive strategies. The global vaccine market is one of the fastest growing segments within the
pharmaceutical industry, expected to double in value by 2024, growing from a $28.3 billion in 2015 to $72.5 billion in 2024 (La Vigne, 2016). Factors contributing toward this rapid growth include more stringent governmental recommendations and growing awareness from consumers (IgeaHub, 2017). Hindering factors include high costs associated with R&D and strict regulatory approval processes. While the scientific and medical consensus on the benefits of vaccination is clear, an omnipresent negative discourse around the safety and efficacy of vaccines continues to play out in social and traditional media. Public concerns and questions around the safety and relevance of vaccines have been on the increase. Vaccine hesitancy, defined as a “delay in acceptance or refusal of vaccines despite availability of vaccine services” (Dubé et al., 2014) is recognised as a growing concern worldwide, affecting high, middle and limited resource settings (Horton & Das, 2011; Larson et al., 2011; Larson et al. 2014). Vaccine hesitancy is closely linked to concerns about the safety of vaccines and people’s perceptions that vaccines are not beneficial (Risk/ Benefit (epidemiological and scientific evidence)). Specific serious adverse events following immunisation (AEFI), such as a death following a vaccination, can trigger hesitancy locally and at a distance if not well managed (SAGE, 2014). The European region has the lowest confidence in vaccine safety with France the least confident globally (Larson et al. 2016). Vaccination coverage gaps persist between countries, as well as within countries. In some countries, coverage of measles-containing vaccine in rural areas is 33% lower than in urban areas.

Vaccine safety
Vaccine safety is a principal concern globally (WHO, 2012a, 2012b), as there is a very high level of safety required for vaccines, particularly since vaccines are usually administered to healthy people, including infants, often covering the vast majority of the population, as immunisation with certain vaccines is mandatory in some countries. Although the use of vaccines is very different from the use of medicines, vaccines are developed, tested, and regulated in a very similar manner, following a standard set of steps. Some of the same safety principles apply, and some of the same institutions are involved in safety surveillance (WHO, 2012). Monitoring vaccine safety is a complicated task (Ellenberg & Chen, 1997). Most countries have AEFI reporting systems, developed and maintained by the national regulatory authority (NRA) and the national immunisation programme (NIP). In Europe, the regulation and
monitoring of vaccines is supervised centrally by the European Medicines Agency (through the Eudravigilance system), in the USA post-licensure monitoring of vaccines is controlled by the Centers for Disease Control and the FDA (through the dedicated Vaccine Adverse Event Reporting System, VAERS). The WHO has established a Global Advisory Committee on Vaccine Safety (WHO, 2013a). Vaccines are thoroughly tested. As in the case of medicinal products, vaccine safety and effectiveness is evaluated diligently during both the pre- and post-licensure stage, with the former relying mainly on laboratory experiments and randomised clinical trials (RCT) and the latter on observational studies, field investigations etc (FDA, 2015; Lopalco, 2012).

Before marketing authorisation, the efficacy and safety of vaccine products are carefully assessed (WHO, 2013a). **Vaccine efficacy** is a measure of the potential of a vaccine to protect from a disease, calculated during controlled clinical trials. It, therefore, describes the protective effect of a vaccine under idealised conditions. Several epidemiological methods can be used to assess vaccine safety in the post-licensure stage, including large cohort studies, household contact studies, case-control studies etc. **Vaccine effectiveness** measures the protective effect of a vaccine under real-life conditions. It denotes the probability that a vaccine, when used in the field under routine vaccination circumstances, confers immunity in a population. Given the low risk tolerance of vaccines, there is a need to balance vaccine efficacy and vaccine safety. Vaccine risk/benefit assessments are utilised extensively to weigh the potential benefits of an effective vaccine against potential risk of an AEFI. **Vaccine benefit evaluation** involves evaluating the size of the reduction in risk of morbidity and mortality from the disease in the vaccinated population, which is dependent on the efficacy of the vaccine used (WHO, 2013a). **Vaccine-associated risk** is the probability of an adverse or unwanted outcome occurring, and the severity of the resulting harm to the health of vaccinated individuals in a defined population, following immunisation with a vaccine under ideal conditions of use (WHO, 2013a). Other important quantitative measures for the evaluation of vaccine include: vaccination coverage, disease burden (incidence, hospitalisation, disability, mortality, financial cost) (Lopalco, 2012).

**Vaccine pharmacovigilance**

Vaccine pharmacovigilance is concerned with monitoring the safety of vaccines in the post-licensure period. According to the CIOMS/WHO Working Group on Vaccine
Pharmacovigilance, **Vaccine Pharmacovigilance** is defined as “the science and activities relating to the ”detection, assessment, understanding and communication of adverse events following immunisation and other vaccine- or immunisation-related issues, and to the prevention of untoward effects of the vaccine or immunisation” (WHO, 2013a). The term **Adverse Event Following Immunisation** (AEFI) denotes adverse reactions linked to vaccination. On rare occasions, adverse reactions can affect the health of vaccine recipients. The goal of vaccine pharmacovigilance is the early detection of and appropriate and timely response to AEFIs in order to minimise negative effects to the health of individuals and lessen the potential negative impact on immunisation of the population.

There are significant commonalities between the practice of pharmacovigilance for medicines and vaccines, although their characteristics and use differ: most medicines are generally used to treat or control diseases among those who have health problems, while vaccines are usually administered to large numbers of healthy people in order to prevent diseases (WHO, 2012a). In this light, vaccines are characterised by a lower level of tolerance for the risk of a side-effects and a much higher standard of safety is expected compared to medications.

Safety issues associated with vaccines may relate to their composition (the active agent, any adjuvant or other ingredients contained), to programmatic or procedural (administration) errors or to vaccinee perception. **Vaccination failure** can be due to vaccine failure (vaccinee- or vaccine-related) or failure to vaccinate appropriately, i.e. that an indicated vaccine was not administered appropriately for any reason (vaccine usage issues or immunisation programme-related issues). Other than vaccine reaction events caused or precipitated by the vaccine when given correctly, more frequently, coincidental health events can follow immunisation and may be wrongly attributed to vaccines. This includes vaccine quality defect; programmatic errors in vaccine preparation, handling, or administration; coincidental events occurring after immunisation but not caused by the vaccine; and immunisation anxiety-related events not linked to the vaccine. In all instances, it is extremely important to detect and analyse promptly serious adverse events following immunisation. A **vaccine safety signal** is information that indicates a potential link between a vaccine and an event previously unknown or incompletely documented, that could affect health, namely new causal associations or new aspect of known associations between a vaccine and an event (WHO, 2017b). Due to the low acceptance of risks, intensive investigation of serious AEFIs is necessary. Steps of vaccine Pharmacovigilance include (Collet
et al., 2000): (a) **signal detection**, suggesting potential association of the AEFI to the vaccination; (b) **hypothesis generation** about causal association between an AEFI and the vaccine); and (c) **hypothesis testing** through appropriate epidemiological methods.

**Causality assessment**

Similarly to medicinal products, when serious AEFI are detected, a causal association needs to be established between an adverse reaction and a vaccine before appropriate mitigation measures are taken (WHO, 1992; 2001). Options for action could include **discontinuing the immunisation campaign, withdrawing a vaccine batch, improving staff training and communication** etc. Vaccine pharmacovigilance comes with many specificities (CIOMS, 2012; Santuccio et al., 2015) and some concepts from causality assessment for medicines cannot be applied. For instance, "dechallenge and rechallenge” and “dose-response” investigations are irrelevant to vaccine pharmacovigilance. Other specificities include that: vaccines are often administered concomitantly; coincidental disease is likely; and adverse events may be caused by immunisation errors. Consequently, determining causation is particularly challenging in the case of vaccines and appropriate methods and a better understanding of signal detection, evaluation, and management in the vaccine and vaccination contexts are needed. The **five principles that underpin the causality assessment of vaccine adverse events are: consistency, strength of association, specificity, temporal relation and biological plausibility** (WHO, 2013a). Several epidemiologic methods have been developed for investigating causality between vaccination and rare adverse events that require data collection only from cases (Lopalco, 2012). An immunisation programme can undergo several stages: pre-vaccine high burden of disease, increasing vaccination coverage, decreasing incidence of disease, emergence of AEFIs, increased focus on AEFIs and loss of confidence, reduction in vaccine coverage and resurgence of the disease, resumption of confidence, and disease eradication (Chen et al., 1994; Chen et al., 2001; Miller, 2015). Continuous **risk-benefit assessment** and **risk management** are required to strengthen the confidence in immunisation programmes and are therefore considered integral to the vaccine pharmacovigilance process. Globally enhanced vaccine safety capacity is required (Chen et al., 2015). In this context, the WHO developed the **Global Vaccine Safety Blueprint** (WHO, 2012a; 2012b), a strategic plan to enable countries to have at least minimal capacity for vaccine safety activities and to enhance their capacity for vaccine safety assessment, and to establish a global vaccine safety support structure.
Strengthening monitoring and surveillance systems, to generate information for decision-making, monitoring the impact of immunisation on morbidity and mortality and changes in disease epidemiology, is among the strategic objectives identified by WHO (2013b) as part of setting up strong immunisation systems. Strategic priorities include leveraging advanced technologies for collection, transmission and analysis of immunisation data to mitigate challenges and extend existing mechanisms for tracking vaccine information and improve vaccine safety communication (Wilson et al., 2014). According to the WHO (2013), AEFI surveillance systems are used to record suspected adverse events associated with the receipt of vaccines, in order to: detect, correct, and prevent programme errors; identify problems with vaccine lots or brand; address false blame from coincidental events; maintain confidence by properly responding to concerns while increasing awareness about vaccine risks; and estimate rates of occurrence on AEFI in the local population. AEFI surveillance systems typically rely on health professionals and consumers spontaneously reporting adverse events that follow immunisation (passive surveillance). Active surveillance methods can also be employed during the post-licensure phase, including clinical trials and formal phase IV surveillance studies or costly studies of large cohorts during extended time periods of several years. Nonetheless, AEFI surveillance systems play a central role in vaccine safety surveillance.

National post-licensure vaccine safety monitoring systems vary considerably in their structure, methods and performance. Some countries have established national systems (The Netherlands, Denmark, Norway, Portugal etc), while in other regional systems exist, covering parts of the country (UK, Belgium, Italy, Spain, Sweden, etc). The WHO (2012a) notes that there is consensus regarding the minimum functions of a national pharmacovigilance system in terms of: collecting and managing reports of adverse drug reactions; identifying signals for drug safety and quality problems; communicating effectively; carrying out risk assessment; maintaining information on medicine prescribing and use, and ensuring that information from pharmacovigilance benefits other health programmes. Surveillance systems are not sufficient, as the type of information they contain is not enough to support the quantification of risks, which is imperative for risk mitigation. For this purpose, Immunisation Information Systems (IIS) or Immunisation Registries need to be consulted. Vaccine safety monitoring principally relies on the use of IIS. Immunisation registries are critical to improving the quality and evaluating the ongoing success of immunisation programs.
National IIS consolidate vaccination records from multiple vaccination providers (Trifirò et al., 2014), and can thus provide comprehensive information about vaccine coverage, safety and effectiveness, help track vaccine call-recall (Pebody, 2012). Johansen et al. (2012) summarise the main uses of immunisation registers as follows (i) collect data on vaccines provided, (ii) generate reminders and recall vaccination notices for each client, (iii) provide official vaccination forms upon request for the individual, and (iv) allow vaccination coverage assessments. IIS data can thus be used to monitor vaccine uptake from national through to local level (vaccination coverage assessments), to identify unvaccinated sub-populations and ensure vaccine uptake is optimal in these pockets and sustain high vaccination coverage. IIS often provide links to other public health surveillance systems.

The need for timely, accurate and complete information is imperative. However, the completeness of immunisation registries is challenged by multiple factors linked to both inherent limitations of these systems and emerging requirements, namely the fragmentation of vaccine administration, the increasing mobility of individuals, new vaccine development, use of multiple products, and increasingly frequent changes in recommendations, (Wilson et al., 2015). Immunisation registries need to be flexible as national vaccine programmes are continuously evolving, with the introduction of new vaccines and changes in current childhood immunisation programmes (Pebody, 2012). Some countries have found difficulties in establishing electronic IISs due to strict data protection laws (Johansen et al., 2012). Immunisation systems are evolving, growing in terms of both scope and methods. The first European Conference on Immunisation Information Systems, held in Stockholm in 2010, concluded that (i) a recommendation to develop a long term EU plan to support Member States to implement immunisation and information systems able to communicate across the EU and (ii) a request to vaccine industry to implement a standardised system for bar coding vaccines to facilitate recording of each vaccination encounter (Johansen et al., 2012). New approaches are needed to improve the efficacy of existing systems. Wilson et al. (2015) proposed the use of mobile technologies as a solution to improve the timeliness and accuracy of immunisation data and engage individuals to have more control of their own immunisation information.

The aggregation and analysis of data coming from different countries presents significant advantages, particularly in the case of rare adverse reactions, as it increases the size of the studied populations. Data heterogeneity represents a key challenge in this process. To facilitate
harmonisation efforts, CIOMS (2012) has produced guidelines for the collection, analysis and presentation of vaccine safety data in surveillance systems. The need of a stronger collaboration among different stakeholders has led to the rise of several networking initiatives in the vaccine domain that bring together heterogeneous partners such as regulatory and public health institutions, academia, companies. Examples include VENICE (for monitoring vaccine policies, practices and coverage), I-MOVE (for evaluating influenza vaccine effectiveness), EUROMOMO (for rapid monitoring of all-cause mortality) ADVANCE (for rapidly assessing and communicating the benefits and risks of vaccines), VAESCO (for evaluating vaccine Safety signals), VSD (the Vaccine Safety Datalink in the USA) (McNeil et al, 2014).
The ADVANCE case study

1. Quality of the ADVANCE project workplan & partnership

The European Union fosters collaborative research across Europe and other partner countries, through ambitious projects by transnational consortia of industry and academia. The Innovative Medicines Initiative (IMI) is working to improve health by speeding up the development of, and patient access to, the next generation of medicines. In this framework, IMI launches open calls for proposals for public-private collaborative research projects targeting specific topics. ADVANCE was selected for funding following an open and competitive two-stage Call for proposals (IMI1 - Call 7), and independent evaluation. The evaluation criteria against which the ADVANCE proposal was assessed include: Scientific and technological excellence (soundness and quality of the scientific and/or technological approach, application of creative and cutting edge methodologies, innovation, progress, scientific and/or technological impact), excellence of the project implementation plan (including adequate and appropriate representation of all relevant stakeholders within the consortium), and excellence of partnership (scientific quality and technological expertise of the individual participants) (IMI, 2017a, 2017b).

The objective of the Call was to “developing framework for rapid assessment of vaccination benefit/risk in Europe”. The IMI1 - Call 7 specifically stresses the importance of public-private collaborative research, arguing that an infrastructure for integrated studies of post-approval benefit/risk can only be developed and sustained by a close interaction between partners from a large horizon, including regulatory agencies, public health institutes, pharmacoepidemiologists and vaccine manufacturers.

Specific requirements set for applicant consortia, as part of the selection process, include:

- Established expertise in areas relevant to the topic;
- Experience and expertise in the regulatory and public health environment and/or capacity to directly engage with the key stakeholders from these environment;
- Engagement of key stakeholder groups (academia, Regulatory agencies, public health organisations, vaccine manufacturers);
• Organisation of proof-of-concept studies with challenging data collection and linkage, analytical methods, and collaborative aspects.

In addition, members of the European Federation of Pharmaceutical Industries and Associations (EFPIA) were committed to collaborate with public and private organisations on the specific topics included in IMI - Call 7. EFPIA represents the pharmaceutical industry operating in Europe, through its direct membership of 36 national associations and 40 leading pharmaceutical companies. The following EFPIA companies are involved in the ADVANCE project:

- GlaxoSmithKline Biologicals S.A, Rixensart, Belgium (7)
- Janssen Vaccines & Prevention B.V, Leiden, Netherlands
- Merck Sharp & Dohme Corp., Whitehouse Station, New Jersey, United States (6)
- Novartis Pharma AG, Basel, Switzerland (4)
- Pfizer Limited, Sandwich, Kent, United Kingdom (3)
- Sanofi Pasteur, Lyon, France (10)
- Takeda Pharmaceuticals International GmbH, Glattpark-Opfikon (Zurich), Switzerland (20)

The number in brackets represents the ranking of each company on the list of “Top pharmaceutical companies with revenue greater than $10 billion” (Wikipedia, 2017). With regards to vaccines, GSK, Merck & Co, Pfizer, and Sanofi were the market leaders in 2016, sharing 88% of the total vaccine market share globally (IgeaHub, 2017).

**EFPIA contribution to the project work**, as stipulated in the Call for proposals, includes:

1. Expertise in post-marketing monitoring, pharmacovigilance, EU regulatory affairs, Quality and Risk Management and government affairs; experience in post-marketing studies in the framework of RMPs; access to databases
2. Experts in observational studies
3. Experts in observational databases, vaccine safety, vaccine effectiveness and benefit/risk, and research pharmacoepidemiology
4. Specialists in pharmacovigilance, observational databases, vaccine effectiveness and benefit/risk, research pharmacoepidemiology and disease epidemiology expertise

Overall, **vaccine manufacturers** bring to the project “their experience in vaccine development, in their specific vaccines, in the challenges, expertise, best practices and standards from their own previous studies as well as their experience in the barriers encountered in implementing their Risk Management Plans” (IMI, 2012).
Furthermore, a number of universities, research organisations, public bodies, non-profit groups are also involved in the ADVANCE partnership. According to Call for proposals, their expected contribution to the project is detailed as follows:

- Academic groups and public health institutes “will provide expertise, especially in developing novel methodology, privileged access to and previous experience with public health data, European-wide collaboration networks, and transparency processes (such as ENCePP)”.
- European Regulatory Agencies “can bring expertise in benefit/risk assessment and knowledge and experience of the information required when faced with challenging decisions when there is uncertainty of the actual risks and benefits of a given vaccine”.

With regards to regulatory agencies, the European Medicines Agency (EMA) is participating in the ADVANCE consortium. EMA is a formal agency of the European Union (EU), and is responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU, serving a market of over 500 million people. EMA coordinates the EU pharmacovigilance system and operates services and processes to support pharmacovigilance in the EU. The Agency is responsible for developing and maintaining EudraVigilance, a system for managing and analysing information on suspected adverse reactions to medicines authorised in the European Economic Area (EEA). Aim of EMA is to foster scientific excellence in the evaluation and supervision of medicines.

**Outreach**

In addition to internal excellence, the establishment of synergies and knowledge exchange with other relevant IMI and European projects is actively sought by the funding authority (IMI). The ADVANCE project has established linked and is further interested in establishing collaborations and the exchange of knowledge with initiatives on benefit-risk monitoring and related areas, in the field of vaccines and other. This includes projects that work on benefit and risk methods, models and data, but also related areas of technical infrastructures and code of conduct, governance and workflows of (multistakeholder) partnerships.

The following section provides a short overview of the ADVANCE project, its scope, objectives and activities.
2. The ADVANCE project

The IMI-ADVANCE project (“Accelerated development of vaccine benefit-risk collaboration in Europe”, www.advance-vaccines.eu) focuses on the development and testing of methods and guidelines for the rapid delivery of reliable data on the benefits and risks of vaccines that are on the market to improve vaccine safety. The project’s guiding vision is to provide the “best evidence at the right time to support decision-making on vaccination in Europe”. In this light, the mission of ADVANCE is “to establish a Blueprint with specifications summarising validated and tested best practice framework that could rapidly provide robust information on vaccine benefits and risks, to support accelerated assessment and decision making” and the overarching aim of the project is “to build an integrated and sustainable framework for the continuous monitoring of the benefit/risk of vaccines”. The goal of the ADVANCE project is to help health professionals, regulatory agencies, public health institutions, vaccine manufacturers and consumers make more informed decisions on benefits and risks of marketed vaccines. To this end, the project is developing the ADVANCE Framework for structured B/R analysis, a set of principles, guidelines and tools to guide decision-makers in selecting, organising, understanding and summarising evidence relevant to benefit-risk decisions.

Although the use of vaccines differs from the use of medicines, similar safety principles apply. Vaccine pharmacovigilance is defined as “the science and activities relating to the detection, assessment, understanding and communication of adverse events following immunisation and other vaccine- or immunisation-related issues, and to the prevention of untoward effects of the vaccine or immunisation”. Essentially, a much higher standard of safety is expected of vaccines, since vaccines are usually administered to large numbers of healthy people and children, and often on a mandatory basis. The post-licensing monitoring of vaccine coverage, effectiveness and safety is very fragmented. Data on vaccine-preventable diseases, vaccination coverage and adverse reactions to vaccines exist in many places and diverse formats, such as electronic health records, disease surveillance systems, and other healthcare databases. The ADVANCE project revolves around the federation of relevant health care databases for safety signal detection and B/R assessment. Its aim is to review, develop and test methods, data sources and procedures which should feed into a blueprint of an efficient and sustainable pan-European framework that can rapidly deliver robust quantitative data for the assessment of the benefits and risks of vaccines that are on the market. ADVANCE aims to build an integrated and collaborative
framework to bring together all relevant stakeholders across the European member states around the topics of vaccines safety and vaccination programs.

The project, which started in October 2013, brings together the European Federation of Pharmaceutical Industries and Associations (EFPIA), the European Medicines Agency and a vast consortium of vaccine manufacturing companies, universities and research organisations, national public health and regulatory bodies, and non-profit groups from 19 European countries. The overall objective is to help health professionals, regulatory agencies, public health institutions, vaccine manufacturers and the general public make more informed decisions on benefits and risks of marketed vaccines. Currently, there is limited capacity in the EU to conduct large scale studies on vaccine exposure, effectiveness and safety, particularly when evaluating rare outcomes, due to difficulty to initiate and conduct multi-country studies; task complexity (since the process involves interactions between multiple stakeholders and lack of confidence; and funding issues and perceived conflicts of interest.

ADVANCE is aimed at developing an infrastructure for integrated studies of post-approval benefit/risk, to address current limitations in vaccine benefit-risk monitoring. Rapid, ad-hoc, vaccine benefit-risk assessment and continuous monitoring pose significant challenges on both a technical and governance level. The ADVANCE project aims to deliver best evidence at the right time to support decision-making, by establishing a validated and tested best practice framework to rapidly provide robust data on vaccine benefits and risks, to support accelerated decision making throughout the life cycle of vaccines. In this process, ADVANCE should accommodate the needs of different stakeholders (e.g. national authorities, insurance companies, regulatory agencies, public health agencies, vaccine manufacturers, health care providers, consumers, etc). Important guiding principles include:

- **Science**: To rapidly deliver the best possible evidence on the research question, using appropriate scientific methods with integrity.
- **Public health**: All decisions to conduct studies and communicate to be guided by the extent to which they serve improving the health of individuals and populations.
- **Transparency**: Disclosure of key decisions and options taken for study design, interpretations of results and conclusions, funding sources, roles of each participant and declarations of interest.
- **Scientific independence**: embedded in provisions of the Code of Conduct.
2.1 Integrated and collaborative framework for vaccine safety

One of the main tasks of the project is to bring together vaccine manufacturers, academics, regulators and health bodies, to allow them to share more data with each other, in order to to pave the way for a framework that will make it easier to rapidly assess the benefits and risks of vaccines.’ The goal of ADVANCE is to review, develop and test methods, data sources and procedures which should feed into a blueprint of an efficient and sustainable pan-European framework that can rapidly deliver robust quantitative data for the assessment of the benefits and risks of vaccines that are on the market. Such a framework would allow regulators and public health authorities to make fast, informed decisions regarding vaccination strategies, and help to maintain public confidence in vaccines, particularly when questions are raised in the media about the safety of specific vaccines. ADVANCE aims to build an integrated and collaborative framework, namely promote a coordinated and harmonised approach involving all stakeholders across the European member states with a stake on benefit and safety of vaccines and vaccination programs. European member states will continue to have their national level approaches. ADVANCE will complement, not replace, activities in place at national level to monitor the benefits and risks of vaccines and build a new platform where data can be analysed and results disseminated to members of the public, especially in moments of crisis. For example, in the measles, mumps and rubella (MMR) vaccine case (Deer, 2011), the ADVANCE platform would have enabled scientists to test the data faster and it would have been easier to determine whether the benefit outweighs the risk. Overall, the ADVANCE collaborative framework is intended to bring added value to: (a) increase statistical power and allow for stratifications to subpopulations; (b) exploit variability in exposure to different types of vaccines and schedules across member states (e.g. adjuvanted versus non-adjuvanted); (c) enlarge research capacity and expertise across the member states; (d) help estimate and understand different results between member states; and (e) help in interpretation of results across member states and support harmonised decision-making.

In this context, the project’s vision statements highlight several objectives: best evidence (scientific validity); right time (faster than current state of the art); integrated methods (multiple stakeholders, multiple data streams, benefit and safety combined); ability to perform monitoring (infrastructure and methods); clear governance rules (code of conduct, ethics, data
protection, regulatory and legal compliance, transparency); and alignment with the common interest (stakeholder satisfaction).

2.2 Data evidence
One of the principal challenges relates to the collection and management of information. With respect to data evidence, vaccine safety draws from different information sources. Some are dedicated for recording data related to vaccines (e.g. immunisation registers for recording administered vaccines), while others are generic health care databases that contain certain information about vaccines, related aspects (e.g. primary care databases) or data that can be mainly used as background information (e.g. population statistics). Additionally, there are surveillance databases that routinely gather data from data sources that could act as data sources for other systems. Recent research work also investigated the potential of social media monitoring for vaccines safety purposes (Thomson, 2015).

For the purposes of the project, data capable of supporting vaccine studies will be obtained from a diverse collection of data sources. As data on vaccine-preventable diseases, vaccination coverage and adverse reactions to vaccines exist in many places and diverse formats, such as electronic health records, disease surveillance systems, and other healthcare databases, first task of the ADVANCE team is to identify and profile data sources (database fingerprinting) capable of yielding rapid access to information on the burden of disease, vaccine coverage, and the benefits and risks of vaccines (de Lusignan et al., 2016). Another challenge for the team is developing the tools to link up this data and analysing it, taking into account the interoperability of the data sources and associated ethical and legal issues. For this reason, central to the work of the project is to set out the framework’s core values, covering issues such as scientific best practice, a code of conduct (Kurz et al., 2015), and rules for interactions (Torcel-Pagnon et al., 2015) between the different stakeholders. Several areas of heterogeneity between Member States have been identified (Denis et al., 2015) with regards to the procedures and the authorities responsible for granting access to data (permission for data access), the authorisation of studies (role of Ethics Committees), the management of personal data etc.

Collected information subsequently feeds into four important analysis dimensions relevant to Benefit/Risk (B/R) assessment and decision making, namely: burden of disease, vaccine
effectiveness, vaccine safety, vaccine coverage, which collectively provide the information for the B/R analysis.

The project work is structured in seven work packages (WPs). The project is based on three main pillars: data sources (WP3), methods (WP4) and best practice mechanisms (WP1). These pillars form an integrated “core triangle” which is strengthened by utilisation of existing results, initiatives and projects through creation of synergies (WP2), validated through selected proof-of-concept studies (POC) (WP5) and leading to the development of a generic blueprint or model for benefit-risk assessment of vaccines in Europe (WP7). The WP6 provides the necessary coordination, management and communication backbone of the project as a whole.

2.3 Proof of Concept studies

The project is scheduled to run a number of proof-of-concept (POC) studies to ensure the platform meets the needs of its intended users. This work falls under WP5 (“Proof-of-concept studies of a framework to perform vaccine benefit-risk monitoring”), with an overall aim to investigate and set the foundations for a holistic framework for knowledge management, so as to promote the development of a smart decision-support environment on the basis of intelligent information processing and integration and validate this approach using specific real-life cases (i.e. a real vaccine B/R question, and/or a case mimicking as much as possible a real life situation that may arise in the vaccine lifetime). In order to cover the most common situations, these studies are designed to cover different age groups (e.g. infants/children, adolescents and adults/elderly), different risk groups (e.g. pregnant women, people with other underlying health problems), and different vaccination scenarios (e.g. vaccinations given annually such as the flu jab, or vaccines introduced into the routine immunisation programme). Focus of the POC studies is to test methods, the IT systems/solutions, measure process performance parameters as indicators to what may be improved, and the acceptance of circumstances (ethical, transparency, Public-private multi-stakeholders interactions). Essentially this work is aimed at investigating the socio-technical ramifications of knowledge discovery from vaccine related information to develop a work process for evidence creation according to the needs of each stakeholder group.

The ADVANCE distributed collaborative information generation workflow (Figure 37) comprises the following stages: Protocol, Data Extraction, Data Transformation and Analysis, Report & Archiving. The process features distributed collaborative information generation
workflow, with common protocol, standardised transformation and shared analyses, while data extraction and original data remain local.

Figure 37: The ADVANCE B/R process flow [source: ADVANCE project]

POC evaluation in the context of ADVANCE focuses on combining, analysing and reporting on the performance and knowledge generated during the performance of the POC experiments, to inform the reliability and sustainability of a post-ADVANCE platform, as defined in the project’s Vision and Mission. Conceptually, **POC evaluation aims to evaluate the “whole system”, including the technology, the framework, and the process used in the POC to perform vaccine B/R assessment.** The POC evaluation will address all aspects of the Evidence Creation Process. Specific validation objectives defined include:

1. Establish the **feasibility of continuously updating the information** on the B/R of a vaccine from the first day after a vaccine is marketed
2. Assess IMI ADVANCE platform for **data availability** on a routinely used vaccine in established vaccination programs covering different populations, and different schedules across countries.
3. Test and assess the **level of collaboration** between different stakeholders in collecting evidence and integrating evidence on the benefits and risks of vaccines
4. Assess the **methods for evidence generation** on safety, effectiveness, preferences and vaccination coverage using a near real-time scenario.
5. Evaluate the **acceptability** of the results by stakeholders for decision making on B/R.

The aim is to decompose and understand the problem: assess the main value drivers of the Benefit-risk analysis and communicate issues in a transparent, rational and consistent way to aid decision making. Evidence on vaccine benefit/risk (typically incidence rates) will be obtained by the targeted studies and synthesised in the B/R-analysis. In literature, there exist several B/R
assessment frameworks, quantitative or descriptive. In the context of ADVANCE analysis is quantitative. Four focus areas are identified for evidence generation, each corresponding to a dedicated working group within WP5. These include: coverage (also looking at vaccination schedules, etc), safety, vaccine effectiveness (primarily targeting direct effects) and preference elicitation. A fifth working group is assigned with evidence synthesis, i.e. developing and running the benefit-risk model.

The information extracted from the databases feeds into the four analysis dimensions relevant Benefit/Risk (B/R) assessment and decision making (burden of disease, vaccine effectiveness, vaccine safety, vaccine coverage). The B/R analyses combining the evidence of the four other streams. The process will result in the development of specific study protocols for the data collection pillars: coverage, preference, benefit, risk and evidence synthesis pillars (B/R analysis). Each of these pillars generates the information using their own methods their own protocol and study team. Individual results feed the B/R assessment pillar, as described in the POC Outline document. Additional information is provided in Sturkenboom et al. (2016).

2.4 First POC study: pertussis vaccine

The first POC study (Sturkenboom et al., 2016; Dahlström et al., 2016) revolves around “Incidence rates of pertussis and pertussis related outcomes of whole-cell pertussis and acellular pertussis vaccines in pre-school children”. The principal research question posed is: “Has the initial benefit-risk profile in children prior to school-entry booster been maintained after the switch from whole-cell pertussis (wP) vaccines to acellular pertussis (aP) vaccines?” The selected study method is a retrospective dynamic cohort analysis to estimate incidence rates of pertussis, conducted utilising electronic healthcare data from ADVANCE partners in Denmark, UK, Netherlands, Spain and Italy (record linkage, surveillance and GP-based databases) that cover an observation period of 15 years. Other (informative) data sources employed include European Centre for Disease Prevention and Control (ECDC) pertussis schedules in Europe and switch points of national ministries of health. The studied variables are Exposures of interest. The investigated outcomes are cases of pertussis disease, complications of pertussis leading to hospitalisation (i.e. pneumonia and seizures) and deaths following pertussis. The specific objectives of the pertussis POC study are summarised in Table 49.
A critical problem facing this investigation is the fact that pertussis vaccine schedules vary largely across Europe. Since the original introduction of pertussis vaccine in the 1940s, many countries have tended to progressively adapt and customise the schedules of their vaccination programs, adding and removing doses, changing ages of primary and booster schedules, with or without catch-up campaigns, and transitioning from wP to aP vaccines for all doses, for one or more booster doses only, or not yet at all. This poses significant challenges on data evidence selection and interpretation. The feasibility assessment of the candidate databases needs to examine whether population, events, and exposure may be misclassified. Following, the study process can proceed to **calculate the rates for coverage, benefits and risks and integrate findings to generate a B/R model of pertussis vaccinations.** The data life-cycle includes:

- **Extraction** of study specific de-identified data from the original databases into study specific common input files. Local data processors extract study specific data into a simple common data model (CDM).

- **Transformation** of the study specific data into analytical datasets suitable for statistical analysis. Using a central scripting approach (based on SAS or R scripts) the extracted data is transformed from CDM files to analytical datasets that can be shared for further analysis on the remote research environment (RRE). Data anonymisation is implemented during this stage. Datasets are upload to the RRE using secure transfer protocols and in encrypted form (e.g. as Jerboa encrypted files).
● **Data analysis** is conducted by statisticians using the OCTOPUS remote research environment (RRE).

The study design is presented in detail in Dahlström, et al. (2016). Two rounds of POC studies are foreseen:

● Phase 1: using databases present in the consortium and following the current state-of-the-art improved processes, focusing on identifying issues and areas of improvement in the system [early Concept design].

● Phase 2: using databases in consortium and potentially others outside the ADVANCE consortium (testing the updated system [Prototype] improved based on the results from Phase 1 POC).
Appendix 3

Detailed process diagrams of the POC1 case study

Figure 38. Process model of the study scoping phase
Figure 39. Process model of the protocol development phase
Figure 40. Protocol development
Appendix 4

Questionnaire - ADVANCE Group Discussions (8th February 2017)

Aim and objectives:

The aim of the meeting with the core group is to discuss using a structured approach and a set of instruments developed in the framework of WP5 for the planning and management of vaccine B/R studies, building on the experience and the lessons learned from the POC 1 study. The objectives of the discussion are:

- To ensure that generic real-scenario processes are in place for the ADVANCE POC 2 study (and its evaluation)
- To eliminate the steps which are not essential during ADVANCE POC 2.

This work responds to the need for better alignment of capabilities and resources, improved collaboration, transparency, and more rigorous management over the POC process. This discussion doesn’t replace any guidance prepared during POC 1 study.

Scope

The overall scope of this exercise is to examine the potential of the two instruments developed in the context of WP5 (process map and planning canvas) to assist the planning and organisation of POC 2 and the generalisation of the ADVANCE framework.

The Process map (and workflow) describes the processes from the scoping to protocol approval (scoping, protocol writing, data sourcing, data extraction, data transformation, analysis, archiving and reporting including additional process which was added for output evaluation and compliance assessment) - covering all the performance indicators listed in ADVANCE evaluation framework, supports the formulation and interpretation of the recommendations, and ultimately strengthens the WP5 proposal for the research process map to progress forward into the ‘ADVANCE blueprint’.

The planning canvas is a planning instrument to be used for each stage of the study to align requirements, capabilities and resources.

Discussions points

Please provide your comments and/or suggestions with regards to the following points:

Point 1: This methodology can be followed easily and intuitively

For example, do you think these instruments are adaptable and extendable based on your experience in the POC 1 study?
Point 2: The Framework captures and represents in concrete dimensions the structural and temporal relations among the underlying socio-technical elements of the investigation system

For example, are the identified dimensions/concepts sufficient? If not, what additional dimensions/concepts should be considered? Does the Framework allow for the analysis of the relationships between concepts?

Point 3: The ADVANCE Framework can be used as a basis for planning and implementing vaccine B/R studies

For example, does the Framework allow to assess the feasibility of a proposed study? Does the Framework allow to define and implement the study protocol? Does the Framework allow to plan and consolidate work across various stakeholders? Does the Framework allow to manage the study execution?

Point 4: The ADVANCE Framework allows in depth investigation of vaccine B/R studies from different perspectives and at different levels of analysis

For example, does this Framework (and toolsets) allow to describe and analyse B/R studies from the perspective(s) and on the level of detail that you need, for example in terms of:

- Scientific, technological, organisational, policy purpose analysis of the life-cycle of B/R study implementations (stage)
- Micro (patient -HCP), Meso (Pharma companies/Intermediary Organisations/National Authorities), Macro (PV) level investigation
- Other need in terms of added values, efficiency and effectiveness - i.e. capacity, flexibility, customisation
Point 5: The ADVANCE Framework can describe any vaccine B/R study (Generalisable and Transferable)

For example, can you name any vaccine B/R study that cannot be described using the ADVANCE Framework? What could be the main issues?

Point 6: The ADVANCE Framework can serve the purposes of continual analysis, to improve/manage change in established vaccine B/R studies and can also serve the purposes of innovation, to help explore and assimilate emerging technology and scientific advances

For example, does the ADVANCE Framework facilitate the management of changes in established study configurations? Does this Framework allow to explore and accommodate new emerging opportunities? (e.g. technology innovations) Does this Framework facilitate the instigation of required changes and innovations?

Does this Framework allow to investigate the applicability potential of emerging innovations?
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