

Title: The Perceptions of Teenagers, Young Adults and Professionals in the participation of Bone Cancer Clinical Trials

Authors:

Susie Pearce, MSc, BSc (Hons), RN

Honorary Health Services Researcher

University College London NHS Foundation Trust, London, United Kingdom.

Email susie.pearce@uclh.nhs.uk

susie_pearce@hotmail.com

Telephone number 01803 361 297

Alexandra Brownsdon, RN, BSc (Hons)

Senior Staff Nurse

Children's and Young People's Cancer Service, University College London Hospitals NHS

Foundation Trust, London, United Kingdom.

Email alexandra.brownsdon@uclh.nhs.uk

Telephone number 0207 794 0500

Fax 0207 317 7566

Lorna Fern, PhD, MSc, BSc (Hons)

Research Development Co-ordinator

National Cancer Research Institute's Teenage and Young Adult Clinical Studies Group,

University College London Hospitals NHS foundation Trust, London, United Kingdom.

Email alexandra.brownsdon@uclh.nhs.uk

Telephone number 0203 447 2168

Faith Gibson, PhD, MSc (Cancer Nursing), RSCN

Clinical Professor in Children and Young People's Cancer Care and Lead of the Centre for Outcomes and Experiences Research in Children's Health, Illness, and Disability (ORCHID) Great Ormond Street Hospital for Children and London South Bank University, London, United Kingdom.

Email faith.gibson@gosh.nhs.uk / faith.gibson@lsbu.ac.uk

Telephone number 0207 8138545

Jeremy Whelan, MD, MBBS, FRCP,

Professor of Cancer Medicine

University College London Cancer Institute and Department of Oncology, University College London Hospitals NHS Foundation Trust, London, United Kingdom.

Email jeremy.whelan@uclh.nhs.uk

Telephone number 0203 447 9346

Fax 0203 380 9055

Verna Lavender, PhD, PGCTHE, BSc(Hons) RGN

Senior Lecturer in Cancer Care

Oxford Brookes University, Oxford, United Kingdom

vlavender@brookes.ac.uk

Tel: 01865 483921

Fax: 01865 482775

Funding

This study was funded by the Bone Cancer Research Trust grant and supported by researchers at the National Institute for Health Research, University College London

Hospitals Biomedical Research Centre, London, England. Verna Lavender was supported by research awards from Oxford Brookes University, Oxford, and Lorna Fern is funded by the Teenage Cancer Trust, United Kingdom.

Declaration of conflicting interests

The authors declare no conflicts of interests with respect to the research, authorship or publication of this article.

Corresponding Author

Susie Pearce

Email: susie_pearce@hotmail.com / susie.pearce@uclh.nhs.uk

Abstract

The reasons why teenagers and young adults with cancer do, or do not, participate in clinical trials is not wholly understood. We explored the perceptions and experiences of young people with bone cancer, and health professionals involved in their care, with regard to participation in two clinical trials. We conducted semi-structured interviews using narrative inquiry with twenty-one young people aged 15 to 24 years and eighteen health professionals. New understandings emerged about perceptions of, and factors that influence participation in, clinical trials. These include perceptions about the importance and design of the clinical trial, communicating with young people in an age-specific manner, using language young people are comfortable with, support from family and peers and specialists in teenage and young adult cancer care. We conclude that addressing these factors may increase acceptability of clinical trials and the trial design for teenagers and young adults with cancer and ultimately improve their participation. Qualitative research has an important place in the development, review and evaluation of clinical trials in ensuring trials are patient centred, and are acceptable and appropriate for teenagers and young adults.

Keywords

Teenager; adolescent; young adult; cancer; narrative inquiry; clinical trial

Introduction

Recruitment to cancer clinical trials is recognised as an indicator of quality care and considered good practice. Clinical trials allow rigorous testing of new treatments with the possibility to impact on improvements in survival for successive generations of cancer patients. Children's cancer care, where five-year survival rates have improved from around 40% in the 1970s to almost 80% for those diagnosed today (Smith *et al.*, 2010), is a notable trial success story largely ascribed to high levels of participation in clinical trials. In England, inclusion of cancer patients in a clinical trial is advocated by health care policy (Department of Health, 2007) and is underpinned by policy specific to children and young people (National Institute for Clinical Excellence, 2005). A number of countries, including the United Kingdom (UK), have reported under-representation of teenagers and young adults (TYA) in cancer clinical trials, when compared to children or older adults. Some researchers have suggested this is associated with lesser survival gains for TYA (Bleyer, 2005; Ferrari and Bleyer, 2007).

The perceived benefit of a clinical trial has been found to positively influence the decision of 12 to 22 year olds and their parents to participate (Read *et al.*, 2009), and the perceived burden of adolescents being asked to participate in a trial soon after a cancer diagnosis has also been reported (Broome *et al.*, 2001). Life stage transition across adolescence and young adulthood (Erikson, 1995; Havighurst, 1972) accompanied by care being delivered across children's and adult's health care settings (Bleyer, 2007) are also reported as factors affecting trial participation in TYA. Quantitative research investigating the role of health professionals in TYA cancer trial participation has previously highlighted the role of organisational factors, for example increased participation in care settings where children's cancer trial protocols are offered compared to care settings where they are not (Parsons *et al.*, 2011; Shochat *et al.*, 2001); and the administrative burden of treating a patient

on a clinical trial (Benjamin *et al.*, 2000). The clinical trial participation of TYA was also found to be negatively influenced by clinicians preference for treatment protocol over the clinical trial (Benjamin *et al.*, 2000; Shaw and Ritchey, 2007).

Interest in TYA with cancer regarding clinical trial participation has recently gained momentum. Barakat *et al.* (2014) set out to understand decision making patterns of 13 young people using semistructured interviews with TYA, parents and health professionals; together with evaluating the Pediatric Research Participation Questionnaire (PRPQ). Barakat *et al.* (2014) reported that young people were not fully involved in decision-making, and suggested that stress, illness and immaturity impaired this. A process to enhance collaborative decision-making through structured diagnostic meetings was recommended. Following development of some questionnaire items, further exploration and validation, they suggest the PRPQ may help address barriers and benefits to trial participation.

Attitudes about clinical trial participation among 15 - 39 year old survivors of lymphoma and leukaemia, and a healthy college sample, were identified using an Attitude Towards Cancer Trial Scales (Grigsby *et al.*, 2014). Fourteen were recruited who had cancer and were offered a clinical trial, of which eight participated. Grigsby *et al.* (2014) reported a positive attitude towards clinical trials; however they also suggested that attitudes to TYA participation were not well understood and might impact on trial participation. They highlighted the need for exploratory work to further understand the complexities of personal, structural and contextual issues that affect cancer trial participation. This echoes recommendations of key authors about adult cancer clinical trials, where they emphasize the importance of qualitative interviews to understand experience (Cox, 1998) and to explore decision making (Cox and Avis, 1996). Understanding patient and professional perceptions of trial entry, along with trial protocol characteristics, have been identified as key to successful accrual (Maslin-Prothero, 2006; Cox and McGarry, 2003).

Although there is growing interest in initiatives to increase enrolment of TYA into clinical studies (Weiss *et al.* 2015), a continuing gap in our understanding of the perceptions and experiences of TYA participating in cancer clinical trials, may continue to hinder progress. We therefore sought to make a further contribution to the emerging evidence by seeking to expand our understanding of the perceptions and experiences of both TYAs and health professionals. To do this, we focused on two clinical trials for bone cancer: EURAMOS-1 (E-1) and Euro- Ewings-99 (E-99). Bone cancer has a peak incidence in this age group, and unlike other cancer types has had less improvement in survival (Bleyer, 2006). The five-year survival rate is 50-60% (Whelan *et al.*, 2012), emphasising the need for further developments in treatment. In recent years, multinational groups have established large, collaborative, research projects to focus on bone sarcomas by undertaking clinical trials across multiple countries, which is a necessity given the rarity of these cancers (Whelan *et al.*, 2015). These trials had ‘appropriate’ age eligibility criteria, including the 15 - 24 age range; however despite the appropriate age eligibility criteria, deficits in accrual of young adults to these clinical trials had still been observed. This suggests factors other than permissive age eligibility are involved (Fern *et al.*, 2014).

Both of these trials were long and complex with a staged consent process; this involved consenting to register on the trial very soon after diagnosis and consenting to randomized treatment after three to four months of chemotherapy. During this initial treatment period, very intense, standard chemotherapy was administered. This usually required extensive periods of hospitalisation, and caused significant side effects with some young people developing complications requiring intensive care or dose limitation. Surgery, which was sometimes extensive and involved amputation of limbs, followed this first course of chemotherapy. Radiotherapy was an additional requirement for many patients with Ewing sarcoma. Consent to treatment randomisation occurred shortly after surgery and pathological

staging of the disease. Randomised treatment varied in intensity and duration for example, it could involve a further eighteen months of treatment or high-dose chemotherapy (a simplified flow diagram of the stages of the trials is shown in Fig.1).

The primary aim of this study was to explore the perception of teenagers, young adults and professionals in participating in bone cancer clinical trials using narrative interviews. To gain a comprehensive, in-depth understanding we gathered data from all stakeholders involved: potential trial participants, recruiting professionals and those who care for young people treated as part of the two clinical trials described. We hoped to gain a deeper understanding of the issues, experiences and perspectives of the stakeholders; identify factors important in trial design; understand the processes and contexts of recruitment; and ultimately contribute to strategies to increase enrolment to clinical studies for TYA.

Methods

Design

A philosophy of interpretive interactionism that supports the study of meaning, which is grounded in the lives of individuals, was adopted for this study (Schwandt, 2000). We conducted interpretive qualitative interviews using narrative methods with all those involved in these two clinical trials. This was to explain and explore the ‘whats’ and ‘hows’ of personal stories to reveal how the meaning of trial participation is constructed over time (Sparkes, 2005). Focussing on both teenage and young adults, and health professionals, allowed for data to be triangulated, attempting to obtain a much deeper and broader understanding of the complexities of *recruiting to* and *participating in* these bone cancer clinical trials (Denzin, 1978; Flick, 1998).

Narrative was used as a method to re-present experience (expressing and reconstituting it) (Squire, 2008). Reissman (2008) suggests narrative encompasses extended

accounts of lives in contexts that develop over the course of single interviews or therapeutic conversations. In this study, narrative allowed the young people and health professionals to have a voice and facilitated the telling of the experience of participating in a clinical trial, the span of which extended over time.

Sample and Setting

We recruited participants with primary bone cancer aged 15 - 24 years at diagnosis from a single, principal TYA treatment centre in the UK. The age range is defined as TYA according to the epidemiological age criteria used in England (NICE, 2005, p13). The setting was a well-developed bone and soft tissue sarcoma centre.

After discussion with the clinical team, we invited all TYA within this age range at diagnosis, and eligible to participate in E1 and EE99 between January 2009 and September 2011, to participate in this study. No TYA were excluded if they fitted these criteria. Twenty-one of thirty-four eligible young people agreed to participate. The TYAs were between six and thirty-two months from diagnosis at the time of interview, the age range was 15-25 years, with a median of 20 years; and fourteen were male. Seven of the young people had Ewing's sarcoma, and were invited to participate in the EE-99 trial; the remaining 14 had osteosarcoma and were invited to participate in the E-1 trial. Nineteen registered on the trials, of those, twelve were eligible for randomized treatment, of which six consented. No TYAs consented to randomized treatment for the EE-99 trial.

We purposefully sampled professionals involved in the recruitment and care of TYA eligible for these trials. The care of TYAs in this principal treatment centre is undertaken across children's and adult oncology services and health professionals were sampled to reflect this service configuration. Professional participants included those directly involved in recruiting TYA into the clinical trials and supporting them during decision-making about

clinical trial participation (including medical oncologists, registrars, clinical nurse specialists and research nurses); and those involved in the care of the TYAs when they were receiving treatment in the clinical trial (including chemotherapy nurses, ambulatory care and oncology ward managers, pharmacists and orthopaedic surgeons). Eighteen, of a total twenty-nine, health professionals invited agreed to participate. Nine professionals were directly involved in recruitment to the two bone cancer trials and nine professional were involved in the care of the TYAs receiving treatment in the trials.

Ethics and Consent

We obtained approval from a National Health Service research ethics committee (study reference: 11/LO/0523). It is worth noting in England that at sixteen a young person is presumed to have capacity to consent to their own treatment (NHS Choices, 2014). We therefore sent letters inviting young people, or their parent if less than 16 years, to directly contact the research team if they wished to opt out and not receive further information.

Young people were sent further information about the study and were later contacted by telephone. We e-mailed invitations to professionals, followed by a telephone call. For those potential participants wanting to participate in our research, we obtained written, informed consent, and assent and parental consent from those less than 16 years old. We assured all participants of anonymity, and that participation would remain confidential and that they could withdraw from the study at any time.

Methods of Data Collection

We used semi-structured narrative interviews to capture the perceptions and experience of all participants. AB conducted interviews using a collaborative, co-participatory process (Fontana and Frey, 2000); providing an opportunity for participants to speak freely of their

experience. An experienced TYA qualitative health researcher SP, supported AB in conducting the interviews. We initially asked the young person to tell their story from when they first heard about the clinical trial, after diagnosis, and then used the questions in a narrative structured interview style to focus on the chronology of events.

We identified open questions and probes from the literature (Lavender V, Watson E, Phillips R and Boulton M, Unpublished). We used reflective probes to paraphrase, encourage depth and demonstrate active listening to facilitate participants to tell their story (Wengraf, 2001). Some examples of probes included 'Can you tell me more about that?' and 'How did that make you feel?' (See Table 1 and Table 2). Prior to data collection we refined the interview schedule with two young people with cancer from the research reference group. Interviews lasted on average 50 minutes. With permission, we digitally recorded and transcribed interviews. Parents, other family members, or friends were present during seven of the young peoples' interviews. Parents actively took part and answered questions in three interviews.

Data Analysis

We analysed transcripts using an interpretative approach similar to that described by (Charmaz, 2000). This included memoing the transcripts, coding and constantly comparing codes to identify categories and themes. We continued this analysis until we had developed an emergent theoretical framework (Charmaz, 2000). We analysed data from TYA and health professional interviews separately. SP and AB read and coded all the transcripts. FG and VL coded a sample of transcripts to validate the coding process. To manage such large volumes of data we began the process of developing an analytical framework following the first interview and through a process of ongoing review and assimilation developed a framework from the additional transcripts and their categories and themes.

After the analytical frameworks were developed, SP and VL returned to the coded transcripts of all the interviews ensuring that nothing had been missed, adding another layer of rigour and review to the process. SP and VL then integrated themes and subcategories of the two analytical frameworks into an integrated analytical framework from both health professional and young person data. This allowed us to follow a thread and actively seek out similarities and differences within, and between, the two data sets (Moran-Ellis *et al.*, 2006). SP and VL used the integrated analytical framework to synthesise key findings of TYA participation in the bone cancer clinical trials.

Results

We identified the following influencing factors across both data sets: perceptions and understanding of clinical trials, communication and information, support and coping, and the context of clinical trials and the culture of TYA specialist care. The influence of these factors on weighing up the benefits and burdens of clinical trial participation were most evident at critical time points of the young person's treatment experience. Participants' narratives highlighted the criticality of registration and randomization, and to some degree the young people reflected on their experience over time. Time and the timing of events seemed significant to all those who participated in the study. We present a balance of interweaved quotes from young people and health professionals and a diagrammatic representation of the findings concludes our paper.

Influencing Factors

Perception of Clinical Trials

Some TYA had learnt about clinical trials in science lessons at school; however for most their knowledge was related either to information given by health professionals or their personal

cancer experience. Some perceived clinical trials as synonymous with chemotherapy; others regarded it as an alternative treatment option. One participant suggested that, “It’s just another way of helping, find different ways to actually cure it faster and get people healthier quicker. So I think when I hear it, it’s like another help, like a helpful organisation.” Some young people who had registered on the clinical trial, did not perceive receiving standard treatment following registration as a clinical trial and instead thought of the clinical trial as being something that happened at, or after, randomisation when trial treatment arms differed:

I didn’t really think about it . . . Like it [being on a trial] only would have made a difference if I’d got to randomisation and they said, “You’re on the one that takes a month longer.” I would, you know, it would just be, “no way”.

Clinical trials were commonly described as being an experiment, with some TYAs describing ‘feeling like a guinea pig’. This was not necessarily perceived negatively, but it was unnerving for some. Terminology used by health professionals may have influenced this perception. One professional discussed the importance of using the term ‘study’ because they thought ‘trial’ sounded experimental and affected patients’ perceptions. This highlights the health professionals’ insight into the possible ways in which terminology might be interpreted by young people. Use of the term ‘rarer cancer’ highlighted the small number of people with this type of tumour and heightened the young person’s sense that every person counted. Young people talked about being aware of the importance of participation in clinical trials: “It’s such a rare thing; they’re really desperate for people to do it.” This understanding probably stemmed from conversations with health professionals, and could be perceived as an additional pressure by the young person. Professionals highlighted the uniqueness of the young person’s diagnosis and the importance of clinical trials. One professional said:

I would start off by saying that, you know, this is a rare cancer that, you know, we know a lot about how to treat it, and we know that because of all the clinical trials that have been done in the past.

The possibility of improving the outcome of the disease for themselves, and the perceived benefit of helping others, outweighed the burden of participation for many of the young people:

If it's a little bit of information for the doctors to work out why it happens, then hopefully it will stop people having cancer, in the future or just create awareness, I don't know . . . I just hope there are benefits for everyone really.

Professionals strongly emphasized the fundamental importance of clinical trials in bone and soft tissue cancer and for TYA where there has been little improvement in outcomes. The perception that clinical trials are vital for improving survival resulted in an emotive response in some professionals. "I wish we had a trial for every patient who, that we would treat... And so I feel frustrated or a failure in a way that we do not have any more, we don't have enough clinical trials open."

Communication and Information

Communication and information, together with support and coping, were central to the experience of trial participation particularly at the times of registration and randomisation. Effective face-to-face communication and information provision was perceived as central for both TYAs and professionals. Face-to-face communication was discussed by the young people as being TYA-centred, reflecting the philosophy of TYA cancer care in the research setting. Professionals spoke about the value of working in a TYA care setting, where there was expertise in talking to young people. One TYA stated, "They didn't talk to me like I was

a child. They spoke to me as if it was my decision, it's my life, it's up to me." Written information was discussed as useful when the young people felt unwell, but they also discussed the fact that they might not feel up to reading. "I might have looked at [the information] for two minutes and thought, Oh I can't read it now, they can do what they want to do."

The language used in the communication with professionals was emphasised. Interpretation of the meaning of 'experiment', 'trial' and 'rare cancer' has already been highlighted. One young person found the use of the word 'cancer' difficult; and 'poor response' used at the time of randomisation provoked a strong, negative reaction in two participants. One participant stated, "Oh for God's sake, I'm not a poor responder, I don't want to be a poor responder." Another was surprised at this choice of wording:

Do you have to call it a 'poor response'? . . . I've gone through so many of the kind of forms of, "How are you feeling, what emotions do you have?" And it is really carefully tailored in terms of wording and things like that. And then you have poor response. It's just something so small can have such a big effect.

Health professionals involved in recruitment of young people to the clinical trials used the term 'poor response' during their interviews as part of their everyday discourse about the clinical trial, and although they expressed anxiety about what the term meant in relation to tumour response, they did not express anxiety about using the term 'poor response' in relation to trial participation.

Enabling trust and building rapport over time, was identified by both TYAs and health professionals, as an important basis to facilitate good communication and ultimately trial decision-making. This was expressed by the young people, "They made you feel really comfortable, they made you feel like at home sort of thing," and by professionals, "It's about

developing the trust . . . between you and the patient. The more time and opportunities you have to do that, is good.” Some professionals were mindful of potential ethical implications of having a close rapport with a patient and then asking them to participate in research. One professional felt, “If you have a good relationship with a patient and you’ve known them over a number of months, then they may sort of subconsciously want to please you and want to do what they think you want them to do.”

Having the opportunity to ask questions was at the core of effective information giving and communication. Professionals spoke about the role of asking questions to be able to ascertain that young people had a full comprehension of the trial and its implications. For young people asking questions facilitated empowerment. “I think the, for me the knowledge was what gave me power and gave me confidence in making decisions and if I didn’t know something, I would ask, they encouraged my questioning.”

All participants perceived dialogue between health professionals and young people was important. The clinical nurse specialist (CNS) role was particularly highly valued by both TYA and other health professionals for their role in communication, information giving, support and coping. One professional stated, “The CNS was the person that I feel is almost like an unbiased party that they can then ask any questions.” Young people discussed how the CNS was able to provide much valued neutrality. It enabled them to work through concerns face-to-face, to simplify the information imparted by professionals, and be an ongoing source of support, “The CNS becomes like your friend, to be honest with you throughout all of this.”

Support and Coping

The support of family, peers, and health professionals was fundamental to young people in being able to comprehend their diagnosis and treatment and cope with decision-making and the treatment experience. For a small number decision-making was family-centred. One

young person described it as, “The family having cancer, the family had osteosarcoma.”

Many professionals discussed family dynamics and the individuality of how families function. Family-centred decision-making was not attributed by professionals to the age of the young person, but more cognitive ability, emotional maturity, the family dynamic, and the young person’s role within the family. For most TYA, the family and others supported decision-making. One young person discussed support in regard to processing information:

Sometimes the words and the terminology that was used was a bit complex, so it was a bit lost in translation! But I think after my mum and dad had explained it to me, because they understood, then it helped me a lot to make more decisions.

Having autonomy in decision-making was crucial for most TYA, “It was my choice. I’m not 16, it’s not meant to be my choice, but it was my choice and no matter what I chose, my parents would stick with me.” For another young person, “I mean, yes you can have advice, advice from someone, but at the end of the day you live and die by your own decisions.” A desire of the young person to protect their parents, by not putting them in a situation where they might feel blamed later, was also recounted:

I would not deem to put the pressure on my parents at all. And I would not put them in a position. You’d be so upset if it was all starting to fall to pieces and you’d be like, “You made me want to go on this clinical trial,” you know.

Sometimes there were differences in views about participation in the clinical trial between the TYA and parents. One professional recounted a difficult experience when one patient at randomisation had said they were doing it because of parental pressure. One young person in our research expressed regret about not participating because of a parents influence:

I said to my dad “I want to do it,” my dad said “What if you do it and get more sick?

You need to make things easier for yourself.” And then, so yes that’s why I said no to that trial.

Young people, talked at length about the importance of hearing and sharing stories with peers who had similar experiences. There was a desire for a ‘buddy’ who was ‘a few steps ahead’ to inspire and give hope to a young person. One young person reflected, “If somebody was to tell me that things would have got better and things get easier, I would have stayed on the trial. But nobody told me that.” Health professionals completely understood the role of peer support, but for them it also raised concerns, “If something goes poorly for somebody, they also hear that.” Nevertheless sharing their stories and experiences with others, and being able to support others, helped the participants know they were not alone and gave them a sense of feeling valued. One TYA described helping the mother of another young person with cancer, “She was really worried because he [her son] was so sick and I explained to her that’s how I was. She said that I was like a guardian angel.”

Context of Care

All the TYA in this study emphasized the importance of being treated in a specialist care setting. Many were treated on a designated young persons’ unit with peers, where there was also access to a wider psychosocial team. This, together with the specialist TYA skills and experience of the health professionals, was central to the experience of young people in this research.

One of the reasons that I’m here [being interviewed about participating in a bone cancer clinical trial] today, one of the reasons that I was able to get through the

treatment with the disposition that I had . . . , was because I was surrounded by people of my own age that I could talk to, that I could help and they could help me. That the nurses and the doctors knew how to talk to me.

Professionals placed high value on working within an organization that prioritized and supported clinical trials.

So, we are prepared to put in the legwork to, you know, to recruit patients. But part of that legwork is about the fact that it will add to your consultation time and you will need more than one consultation. . . . I think if you've got a big, well-resourced unit, then you are going to be able to put young people into trials.

Working within a team to provide timely support and information; feeling supported themselves by the team; and developing communication skills as a team were discussed in depth. Professional and organizational factors, such as team working and efficient infrastructure, were perceived by the health professionals as facilitating a culture that was conducive for the participation of TYA in bone cancer trials.

Critical Time Points

Registering on a Clinical Trial

Young people were typically registered on the trials within two weeks of receiving their cancer diagnosis, with discussions starting from the point of diagnosis. The timing of this was difficult for all young people. One young person described their thoughts about this, "Oh this is another decision I've got to make, you know, I don't really want to – I'm not interested. . . . Why give someone this kind of decision when all this is going on already." Young people who had experienced a prolonged diagnostic journey felt a sense of urgency to start

treatment. Pressure from the professionals to commence treatment was also experienced. One young person explained, “I was quite rushed into it. But that was only because they wanted to start my treatment really straightaway.”

Ensuring that information was shared and understood, and consent was informed at this time, was perceived by some professional groups, such as research nurses, as difficult for both TYA and themselves professionally. One health care professional expressed, “I think a lot of the time it’s just too much information to take in. And I think the ones that turn it down, it is just too much.” Others, particularly medical professionals, directly responsible for obtaining consent, perceived registration as easier than randomisation. At registration they were explaining the opportunity to register on a trial initially with standard treatment and opt out at a later date. Some TYA decided to register for the trial at this stage for this reason, “We can make the decision to drop out. But we can’t make a decision to drop in. So leave all doors available, all options open.” For others there was a strong sense of wanting to participate. Either to get better, “[I] just wanted to be well. I think even if I didn’t understand, I would accept ... I didn’t want to have this pain again,” or to help others, “If I can be part of a trial and make something, find a better way for people to be treated or an easier way to be treated, I don’t mind being that guinea pig.”

Professionals also recognised altruism as a motivating factor, “Generally the people are quite interested in taking part in research to help, to help other patients in the future really, if not for themselves.” The timing of conversations was crucial; professionals recognised individual’s distress at receiving a cancer diagnosis and during the registration process they consistently emphasized the importance of giving young people sufficient time and plenty of opportunities for communication, information and support.

Randomisation

Randomisation was expressed by most TYA and health professionals as the point when critical decisions were made. Consent to randomisation for both trials took place following surgery. Eligibility to the treatment arm of the clinical trials depended on treatment response. One professional explained, “If the patient had a poor response that is going to be a harder conversation to have.”

This professional went on to explain the irony that although the good response conversation was the easiest to have, TYAs whose disease had responded well were often happier to stay with standard treatment and were less keen to be randomised. For many it was not an easy decision. One TYA described the anguish:

It was like, “you’ve had a poor histological response. And like what do you want to [do]?” I couldn’t make my mind up at the time, because in my head I had four months more left of treatment and I was looking at this longer one, it was like double the time. And more drugs as well. I was like, “oh my God, I don’t know”. . . . I stood outside by the lifts and I was just thinking like, “oh my God what am I going to do?”

Some TYAs found the concept of randomisation and the concept of clinical equipoise difficult to comprehend. Being asked to make a (sometimes difficult) decision about receiving the treatment arm, when it was ultimately dependent upon a random computerised event took time for some young people to make sense of: "I wanted to go on the trial, so the randomisation was a bit of a pointless thing to me, but then at the end of the day it gives everyone a chance to be on the trial".

Others described how they would have felt disappointed if they had not received the experimental treatment arm, or would have preferred the professionals to make a decision for them. Despite the desire for control over choice of a treatment arm, both TYA and health

professionals felt that the young people had better comprehension of what was involved, what treatment was like, and that decision-making and randomisation, if not easy, was more informed.

The decision-making process at randomisation involved weighing up the benefits and burdens of the treatment (See Fig. 2). Extended periods of hospitalisation were perceived as an unacceptable burden for many young people. Many needed to stay in hospital between chemotherapy treatments because of toxicities, which considerably limited the amount of time they were at home, “If you can imagine that four out of the five weeks I was in hospital, and even when I wasn’t in hospital, I felt I had a massive hangover from the worst night out you’ve probably ever had.”

Toxicity from the treatment was very powerfully described by many young people. A number were treated in intensive care units for treatment-related toxicity and a few had treatment toxicities that were dose-limiting or resulted in treatment cessation. The burdensome nature of treatment for bone sarcomas was fully understood and appreciated by the health professionals:

You know, they’re probably some of the hardest chemotherapy regimens that I’ve ever worked with – that in itself without adding extra ten weeks or a couple of months to their sort of treatment time you know with some of them they are kind of, “Okay I’ve had enough”.

Most young people expressed a desire to return to a normal life. One reflected how the sense of lost time is perhaps more acute for a younger person, when so much [change] is happening, than an older person. She said:

I can’t see there’s an easy way to entice a young person into a clinical trial, because a young person is still young. If I was 50 then I probably would have done it, you know,

probably it wouldn't bother you to have that extra time. But for someone who is growing up fast, life's too short.

Discussion

This is the first qualitative study that integrates data from TYAs with cancer and health professionals involved in their care, about *recruitment to*, and *participation in* clinical trials. Similar to other reports, our findings illustrate the multi-factorial nature of the experience of participating in clinical trials together with the ongoing decision-making process (Biedrzycki, 2010). We identified influencing factors and critical time points for young people eligible to participate in these two clinical trials (See Fig. 2).

The time of clinical trial registration soon after diagnosis when there was an imperative to start treatment urgently, was felt by many TYA and health professionals to be challenging; this is similar to other findings (Broome *et al.*, 2001). In addition, consultations about consenting to randomised treatment coincided with difficult discussions about treatment response, although there was a sense that having experienced treatment the young people were more informed.

We found that the prospect of prolonged treatment duration or increased treatment intensity on the experimental treatment arm often influenced the decision to participate. Adolescence and young adulthood compounded the sense of intensity and longevity of treatment for many TYA; they expressed urgency 'to get on with life' and referred to the poignancy of 'wasted time'.

Previous research with TYA highlights the importance of perceived benefits of participating in research to self (Broome *et al.*, 2001) and others (Hendricks-Ferguson *et al.*, 2013), as central in decision-making. In this study benefit to self carries special meaning in

the context of cancer clinical trials, where treatments may have significant adverse effects and survival is dependent on treatment effectiveness. Altruism was expressed as a reason to participate in both the bone cancer clinical trial and our research. The benefit for others often outweighed the burdens of trial participation for the young people.

Young people valued being placed at the centre of communication, which supported autonomous decision-making and reflected a highly-evolved model of multidisciplinary TYA cancer care (Kelly *et al.*, 2004). Our findings contrast with findings reported by (Barakat *et al.*, 2014) that TYA perceived low involvement in making decisions about clinical trial participation. The young peoples' accounts of language and communication used by professionals, suggests that both written and verbal communication are important influencers on their perception of clinical trials.

The value of the CNS as a support mechanism was evident and should be considered in strategies to enhance trial participation. The CNS was perceived by both young people and professionals as an essential party, being regarded as a 'neutral friend'; trust, support and rapport developed over time with other staff including key medical staff was also highly valued. These relational aspects of care could, however, have the potential to generate conflicts of interest when obtaining clinical trial consent. It is essential for health professionals to work within ethical frameworks and develop high levels of awareness and reflexivity within themselves and across teams (Finlay and Gough, 2003).

Our findings also illustrate the importance of support from, and support for, peers participating in the same clinical trial. Peer support is an aspect of care that is central to specialist TYA cancer care philosophy (Tai *et al.*, 2014).

Reflections on the study: strengths and limitations

Using a narrative approach facilitated the young people to reflect on their experience over time. The stories shared in this study highlighted that the young people perceived the clinical trial as their treatment, rather than part of their treatment. Some young people expressed regret about not choosing to enter the randomised phase of the trial. The psychological effects of decision-making in terms of regret and guilt have been found in other studies (Biedrzycki, 2010; Stevens and Ahmedzai, 2004). For others, participating in the clinical trial and/ or having chemotherapy treatment marked a poignant period in their life story and participating in our research provided an opportunity for reflection. Some young people were still in one of the two clinical trials, some were two years after treatment. Of these a few were struggling to cope with life after cancer treatment. Two TYA had relapsed and one was receiving palliative treatment. These different time periods from data collection to when the TYA participated in the trials is a limitation of this research. Prospective longitudinal research, such as that by Stevens and Ahmedzai (2004), would allow the exploration of experience over time.

Parents were present in some interviews. Although not actively encouraged, this could be seen as a reflection of the model of TYA cancer care, communicating with TYA within the context of the whole family, and the reality for professionals in clinical trial recruitment. The researcher who conducted the interviews, similar to the health professionals recruited to this research, kept the young person at the centre and prioritised their autonomy. However, there was flexibility to individual needs and dynamics and occasionally the parent took a participatory role in the conversational-style interview.

Using a narrative approach provided the participants of this study with an equal voice. Our findings reinforce the importance of hearing the perspective of both the young people and the health professionals who managed their care. Triangulating the data by integrating data sets from young people and health professional's added rigour to our study design, in addition to credibility, dependability and depth of the findings. The analysis was conducted

by four members of the research team, none of whom had involvement with the clinical team, which added further dependability and trustworthiness to our findings.

The setting for this study was a well-developed specialist TYA cancer centre, and thus had well-established multidisciplinary teams, focusing on treatment, trials, and psychosocial and developmental aspects of TYA cancer care. It is important to acknowledge the different contexts in which young people with cancer are cared for, although TYA with bone cancer would usually be treated in similar contexts in the UK. Recruiting participants from one hospital, together with using an opt-out recruitment process to promote autonomous decision-making and minimise potential gate-keeping (LeBlanc *et al.*, 2013), might have aided recruitment to our research.

Implications for research

Fern *et al.* (2014) suggest an increase in TYA participation between 2005 and 2010 can be attributed to five key criteria, the five A's: Availability, Accessibility, Awareness, Appropriateness and Acceptability. They describe barriers and facilitators including: awareness of trials by both patients and health professionals; availability of open studies that TYA are eligible for; accessibility of the trial; appropriate trial design with age eligibility criteria that is permissive of inclusion of young people; and the acceptability of trial design for both patients and health professionals. Our study reinforces key messages in this publication and strengthens the call for the involvement of young people and indeed professionals in trial design at the outset. The National Institute for Health Research (NIHR, 2015) suggest that one method to do this is to involve patients as members of the research study group. However, there is concern that patient and public engagement in research, for example attending research advisory board meetings to discuss acceptability of the design of research studies, can be tokenistic and better methods of engaging stakeholders in research are still needed (Domecq *et al.*, 2014).

The use of qualitative research to engage stakeholders early in trial design is recommended by Barakat *et al.* (2014) and Woolfall *et al.* (2014). Our study demonstrates use of qualitative research before or alongside clinical trials is central to developing a deeper understanding of the acceptability of a clinical trial based on stakeholder perspectives and experiences.

Concluding thoughts

This qualitative study provides a deeper understanding of the perceptions and experiences of key stakeholders in TYA cancer trials. It has identified factors important in trial design and as such contributes to an increasing awareness of the importance of both processes and contexts of recruitment to both trial design and treatment delivery. Our study also emphasises a role for qualitative research in clinical trials, from early stages of trial design to ongoing evaluation and review, to ensure trials are patient centred. We hope these findings alongside further research will ultimately contribute to strategies that increase enrolment and retention to clinical studies for TYA, with our primary aim being to improve young peoples' outcomes from cancer that we know are influenced by participation in clinical trials.

Acknowledgements

We thank all the patients and health professionals who participated in this study. We would also like to thank the Bone Cancer Research Trust for funding this study, and the National Institute for Health Research, University College London Hospitals Biomedical Research Centre, Oxford Brookes University, and the Teenage Cancer Trust for financially supporting some of the researchers who conducted this research.

References

- Barakat, L., Schwartz, L.A., Reilly, A., Deatricks, J.A., and Balis, F. (2014) A qualitative study of phase III cancer clinical trial enrollment decision-making: Perspectives from adolescents, young adults, caregivers, and providers. *Journal of Adolescent and Young Adult Oncology*, **3**, 3-11.
- Benjamin, S., Kroll, M.E., Cartwright, R.A., Clough, J.V., Gorst, D.W., Proctor, S. J., *et al.* (2000) Haematologists' approaches to the management of adolescents and young adults with acute leukaemia. *Br J Haematol*, **111**, 1045-1050.
- Biedrzycki, B.A. (2010) Decision making for cancer clinical trial participation: a systematic review. *Oncol Nurs Forum*, **37**, E387-399.
- Bleyer, A. (2005) The adolescent and young adult gap in cancer care and outcome. *Current Problems in Pediatric and Adolescent Health Care*, **35**, 182-217.
- Bleyer, A. (2007) Adolescent and young adult (AYA) oncology: the first A. *Pediatr Hematol Oncol*, **24**, 325-336.
- Bleyer, A., Barr, R., and Ries, L.A.G. (Eds). (2006) *Cancer Epidemiology in Older Adolescents and Young Adults 15 to 29 Years of Age, Including SEER Incidence and Survival: 1975-2000*. Bethesda, Maryland NIH.
- Broome, M.E., Richards, D.J. and Hall, J.M. (2001) Children in research: the experience of ill children and adolescents. *Journal of Family Nursing*, **7**, 32-49.
- Charmaz, K. (2000) Grounded theory objectivist and constructivist methods. In: Denzin, N.A. and Lincoln, Y.S. (ed) *Handbook of qualitative research*. 2nd ed. Thousand Oaks: Sage Publications, 509-536.
- Cox, K. (1998) Investigating psychosocial aspects of participation in early anti-cancer drug trials: towards a choice of methodology. *Journal of Advanced Nursing*, **27**, 488 - 496.
- Cox, K. and Avis, M. (1996) Psychosocial aspects of participation in early anticancer drug trials: Report of a pilot study. *Cancer Nursing*, **19**, 177-186.
- Cox, K. and McGarry, J. (2003) Why patients dont take part in cancer clinical trials: an overview of the literature. *European Journal of Cancer Care*, **12**, 114-122.
- Denzin, N.K. (1978) *The Research Act*, New York: McGraw Hill.
- Department of Health (2007) *Cancer Reform Strategy*. London: DH.
- Domecq, J.P., Prutsky, G., Elraiyah, T, Wang, Z., Nabhan, M., Shippee, N. *et al.* (2014) Patient engagement in research: a systematic review. *BMC Health Serv Res* **14**, 89.
- Erikson, E.H. (1995) *Childhood and Society*: Vintage Books, London.
- Ferrari, A. and Bleyer, A. (2007) Participation of adolescents with cancer in clinical trials. *Cancer Treatment Reviews*, **33**, 603-608.
- Fern, L.A., Lewandowski, J.A., Coxon, K.M., and Whelan, J. (2014) Available, accessible, aware, appropriate, and acceptable: a strategy to improve participation of teenagers and young adults in cancer trials. *The Lancet Oncology*, **15**, e341-e350.
- Finlay, L. and Gough, B. (2003) *Reflexivity: A Practical Guide for Researchers in Health and Social Sciences*, Oxford, UK: Blackwell Science Ltd.
- Flick, U. (1998) *An introduction to qualitative research: Theory methods and applications*. London: Sage Publications.
- Fontana, A. and Frey, J.H. (2000) The interview: from structured questions to negotiated text. In: YS DNAL (ed) *Handbook of qualitative research*. 2nd ed. Thousand Oaks: Sage Publications, 645-672.
- Grigsby, T., Kent, E.E., Montoya, M.J., Sender, L.S., Morris, R.A., Ziogas, A., and Anton-Culver, H. (2014) Attitudes Toward Cancer Clinical Trial Participation in Young Adults with a History of Cancer and a Healthy College Student Sample: A

- Preliminary Investigation. *Journal of Adolescent and Young Adult Oncology*, **1**, 20-27.
- Havighurst, R. (1972) *Developmental tasks and education*, New York: David McKay Co Inc.
- Hendricks-Ferguson, V.L., Cherven, B.O., Burns, D.S., Docherty, S.L., Phillips-Salimi, C.R., Roll, L., et al. (2013) Recruitment strategies and rates of a multi-site behavioral intervention for adolescents and young adults with cancer. *J Pediatr Health Care*, **27**, 434-442.
- Kelly, D., Pearce, S., and Mulhall, A. (2004) 'Being in the same boat' ethnographic insights into an adolescent teenage unit. *International Journal of Nursing Studies*, **41**, 857 - 857.
- LeBlanc, T.W., Lodato, J.E., Currow, D.C., and Abernethy, A.P. (2013) Overcoming recruitment challenges in palliative care clinical trials. *J Oncol Pract* **9**, 277-282.
- Maslin-Prothero, S. (2006) The role of the multidisciplinary team in recruiting to cancer clinical trials. *European Journal of Cancer Care*, **15**, 146-154
- Moran-Ellis, J., Alexander, V.D., Cronin, A., Dickinson, M., Fielding, J., Slaney, J. and Thomas, H. (2006) Triangulation and integration: processes, claims and implications. *Qualitative Research*, **6**, 45 - 49.
- NHS Choices (2014) *Consent to Treatment - Children and Young People*. Available at: <http://www.nhs.uk/Conditions/consent-to-treatment/Pages/children-under-16.aspx> (accessed October, 2015)
- National Institute for Health and Clinical Excellence. (2005) *Guidance on Cancer Services: Improving Outcomes in Children and Young People with Cancer, The Manual*. London: NICE.
- National Institute for Health Research. (2015) *How to Involve Patients in Your Research*. Available at: <https://www.crn.nihr.ac.uk/can-help/funders-academics/our-ppi-offering-to-the-research-community/> (accessed October 2015).
- Parsons, H.M., Harlan, L.C., Seibel, N.L., Stevens, J.L., and Keegan, T.H.M. (2011) Clinical Trial Participation and Time to Treatment Among Adolescents and Young Adults With Cancer: Does Age at Diagnosis or Insurance Make a Difference? *Journal of Clinical Oncology*, **29**, 4045-4053.
- Read, K., Fernandez, C.V., Gao, J., Strahlendorf, C., Moghrabi, A., Pentz, R. D., et al. (2009) Decision-making by adolescents and parents of children with cancer regarding health research participation. *Pediatrics*, **124**, 959-965.
- Reissman, C.K. (2008) *Narrative Methods for the Human Sciences*, London, England: Sage Publications Ltd.
- Schwandt, T.A. (2000) Three epistemological stances for qualitative inquiry: interpretivism, hermeneutics, and social construction. In: Denzin NK, Lincoln, Y.S. (ed) *Handbook of qualitative research*. 2nd ed. Thousand Oaks, CA: Sage Publications, 189- 213.
- Shaw, P.H. and Ritchey, A.K. (2007) Different rates of clinical trial enrollment between adolescents and young adults aged 15 to 22 years old and children under 15 years old with cancer at a children's hospital. *J Pediatr Hematol Oncol*, **29**, 811-814.
- Shochat, S.J., Fremgen, A.M., Murphy, S.B., Hutchison, C., Donaldson, S.S., Haase, G.M., et al. (2001) Childhood cancer: patterns of protocol participation in a national survey. *CA Cancer J Clin*, **51**, 119-130.
- Smith, M.A., Seibel, N.L., Altekruuse, S.F., Ries, L.A.G., Melbert, D.L., O'Leary, M., et al. (2010) Outcomes for Children and Adolescents With Cancer: Challenges for the Twenty-First Century. *Journal of Clinical Oncology*, **28**, 2625-2634.
- Sparkes, A. (2005) Narrative analysis: exploring the whats and hows of personal experience. In: I H (ed) *Qualitative research in health care*. Berkshire: Open University Press, 191-209.

- Squire, C. (2008) From experience-centred to socio-culturally narrative approaches to narrative. In: Andrews MS, C. Tamboukou, M. (ed) *Doing Narrative Research*. London, England: Sage Publications Ltd.
- Stevens, T. and Ahmedzai, S.H. (2004) Why do breast cancer patients decline entry into randomised trials and how do they feel about their decision later: A prospective, longitudinal, in-depth interview study. *Patient Education and Counseling*, **52**, 341-348.
- Tai, E., Beaupin, L. and Bleyer, A. (2014) Clinical Trial Enrollment Among Adolescents With Cancer: Supplement Overview. *Pediatrics*, **133**, S85 - S89.
- Weiss, A.R., Hayes-Lattin, B., Kutny, M.A., Stock, W., Stegenga, K. AND Freyer, D.R. *et al.* (2015) Inclusion of Adolescents and Young Adults in Cancer Clinical Trials. *Semin Oncol Nurs*, **31**, 197-205.
- Wengraf, T. (2001) *Qualitative research interviewing*. London: Sage.
- Whelan, J., McTiernan, A., Cooper, N., Wong, Y.K., Francis, M., Vernon, S., *et al.* (2012) Incidence and survival of malignant bone sarcomas in England 1979–2007. *International Journal of Cancer*, **131**, E508-E517.
- Whelan, J.S., Bielack, S.S., Marina, N., Smeland, S., Jovic, G., Hook, J. M., *et al.* (2015) EURAMOS-1, an international randomised study for osteosarcoma: results from pre-randomisation treatment. *Ann Oncol*, **26**, 407-414.
- Woolfall K, Young, B., Frith, L., Appleton, R., Iyer, A, Messahel, S., Hickey, H. and Gamble, C. (2014) Doing challenging research studies in a patient-centred way: a qualitative study to inform a randomised controlled trial in the paediatric emergency care setting. *British Medical Journal Open*, **4**, 1 - 11.

Table 1. Examples TYA Interview Questions

Question Area	Examples of Questions
Background	<p>Can you tell me a bit about yourself?</p> <p>Can you tell me a bit about what is going on with you now?</p> <p>Can you tell me about the treatment you have had?</p>
Knowledge of clinical trials	<p>Can you tell me what you understand about the term clinical trials?</p> <p>What do you think about them?</p>
Registering on a clinical trial	<p>Do you remember being asked to take part in the clinical trial?</p> <p>Can you tell me a bit more about this, such as who you were with and how long was it since your diagnosis when you were asked?</p> <p>Do you remember who you spoke to about it?</p> <p>How did you feel about being asked to make that decision?</p> <p>What did you decide to do?</p> <p>What did you find helpful/ unhelpful?</p>
Randomization on the clinical trial (for those who were eligible)	<p>Was there anything different about deciding to being randomized from the time of registration?</p> <p>Can you tell me what happened, what you decided and how?</p>
Time of potential randomization for all	<p>What was happening for you at this time?</p> <p>How did you feel about the trial/ treatment and things in general at his time?</p> <p>How have been things since?</p>
Reflecting back	<p>Reflecting back what, if anything, could have been differently?</p> <p>What was particularly helpful?</p> <p>What do you think could help young people?</p> <p>What advice would you give them?</p> <p>What advice would you give professionals?</p> <p>Overall what are your thoughts and feelings of clinical trials and your experience of them now?</p>

Table 2. Examples of Health Professional Interview Questions

Question Area	Example of Questions
Background	<p>Can you tell me a little bit about your role (in the care of patients with bone cancers/ soft tissue tumours)?</p> <p>What involvement do you have with the bone sarcoma clinical trials?</p> <p>How long have you been involved with these trials/ caring for people undergoing these trials?</p>
Knowledge of clinical trials	<p>What do you understand about clinical trials in general?</p> <p>What are your thoughts about treating patients on clinical trials?</p>
TYA and bone cancer trials	<p>What do you think are the specific issues around recruiting young people (15-24 year olds) with cancer to clinical trials?</p> <p>What is your understanding of the bone cancer specific trials, Euramos-1 and EE-99?</p> <p>What do you perceive are factors that influence participation in Euramos-1 and EE-99 for TYA?</p>
Process of recruitment and randomization (for those involved)	<p>Can you tell me about how TYA patients are recruited to the bone sarcoma clinical trials?</p> <p>Can you tell me what you discuss when talking to young people or their parents, about consenting to the clinical trials?</p> <p>What happens at randomization?</p> <p>What support is there for patients making decisions about entering these clinical trials?</p> <p>How do you feel about discussing randomisation?</p> <p>How is discussing randomisation different from registration and the initial consultation?</p>
Reflections	<p>What sorts of things do you think (would) help support young people through the clinical trial?</p> <p>What do you think might support the professionals involved in this process?</p>

Legend for Figure 1 Twenty-one teenagers and young adults aged 15 – 24 were eligible to participate in either the Euro Ewing-99 or Euramos-1 clinical trials. The simplified design of the clinical trial is shown in treatment stages. The number of young people that consented to each stage of these two clinical trials are shown in brackets.

Legend for Figure 2 Critical time points were experienced at times of consent decisions about clinical trial registration and randomisation. Young people on both clinical trials received treatment between the times of registration and randomisation, which was an influencing factor on consenting to randomised treatment. Perceptions of clinical trials, communication and information, support and coping, and the culture of TYA cancer care, were found to be influencing factors on weighing up the benefit and burden to participating in the clinical trial.

Figure 1. Treatment received by young people recruited to this study

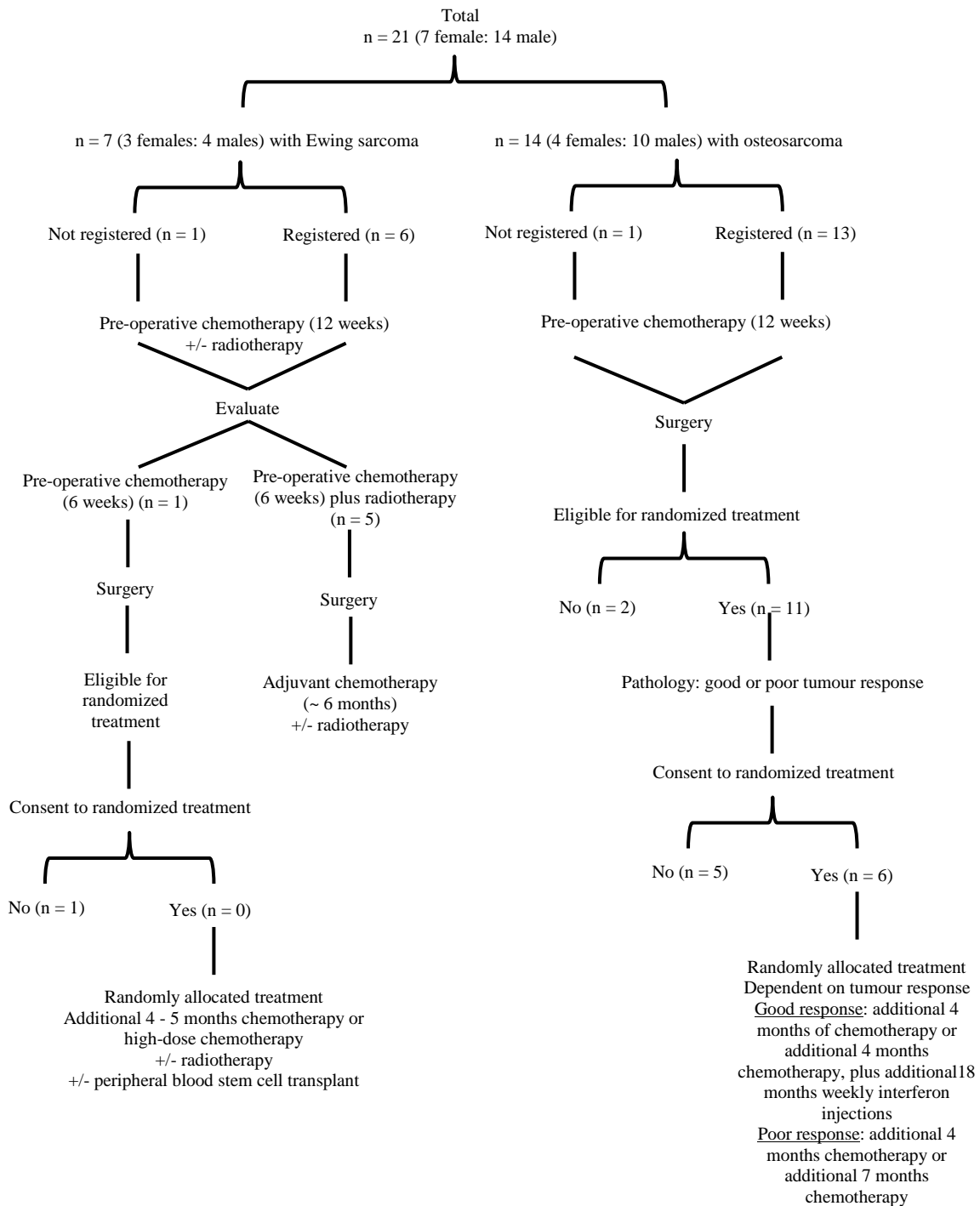


Figure 2. Diagrammatic representation of influencing factors and critical time points in TYA bone cancer clinical trial participation

