DESIGNING AND CONDUCTING FEASIBLE AND ACCEPTABLE PHARMACOKINETIC RESEARCH IN CRITICALLY ILL CHILDREN: A MIXED METHODS STUDY

BY
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Abstract

Introduction: Despite the importance of pharmacokinetic (PK) information for patient management there are low numbers of paediatric PK studies and little guidance available on optimum study design and conduct.

Method: Drawing on Implementation Science, a mixed-methods study was conducted, including a scoping review (SR) (PK literature: 1990-2015) and quantitative and qualitative inquiry (stakeholders: lay population, service users and health-care professionals). Aim: to explore the feasibility and acceptability of paediatric PK research.

Results: The SR (203 papers) highlighted significant problems with participant recruitment, retention and sampling. Stakeholders (n=240) added insight into these phenomenon, with lack of research staff, additional blood-sampling and appointments highlighted as significant barriers to recruitment and conduct. Facilitators included sensitivity and timeliness of approach, communication, involvement of child/young person (CYP) in decision-making, engagement between research and clinical teams, reassurance of safety, pain minimisation, and avoidance/reduction of burden to the CYP and family. Dedicated research support was viewed as critical to success.

Discussion: PK research was viewed as feasible and acceptable by service users and health professionals, even in the context of critical illness. Novel, evidence-based, patient-centred, recommendations for future PK study conduct and design have been generated which are applicable for those designing, approving and implementing PK research.

Dedication

This work is dedicated to Ben, Rory and Camille, my amazing family.

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Publications

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Chapter 1. Introduction

1.1 Paediatric medicines

Children and young people (CYP) have a fundamental right to safe and effective medicines (Royal College Paedatrics and Child Health, 2004, Choonara and Sammons, 2014). In the past infants and children have suffered serious harm because of exposure to inadequately investigated medications (Sutcliffe, 2003, Kemper et al., 2011). A number of studies have established the widespread use of off-label medicines (outside of the license with respect to dose, route of administration, indication, contraindication or age of a recipient) or as an unlicensed preparation (Turner et al., 1996, Turner et al., 1998, Conroy et al., 2000, 't Jong et al., 2001, O'Donnell et l., 2002, Barr et al., 2002). The consequences of this are prescribers often have no alternative but to resort to off-label products, without evidence based information to guide them in assessment of the risks and benefits of the medicine (Turner et al., 1999, Conroy et al., 1999, Conroy et al., 2000, Vermeulen et al., 2017). This places CYP at risk of harm (European Medicines Agency, 2004). Wherever possible, doses should not simply be scaled linearly from a known adult dose (Royal College Paedatrics and Child Health, 2004, Bartelink et al., 2006, Anderson, 2011, Vermeulen et al., 2017). Childhood is characterised by periods of rapid growth, maturation and development and many physiological changes occur which have an impact on the absorption, distribution and elimination of medicines (Nunn and Williams, 2005, Kemper et al., 2011, Batchelor and Marriott., 2014). Safe and effective prescribing in children is impossible without a fundamental understanding of how development influences variables such as hepatic enzyme systems, renal clearance of drugs and their metabolites and relative size of body compartments (Anand et al., 2005, Tod et al., 2008, Batchelor and Marriott, 2014). PK

research should be performed in different age groups to support formulation development and determine the PK parameters to support dosing recommendations (ICH E11 guidelines) (European Medicines Agency, 2001). Research is also required in diseases which are unique to CYP, where the relevant knowledge cannot be obtained by research with adults or where the trajectory of the disease is different from that in adults (Royal College of Paediatrics and Child Health Ethics Advisory Committee, 2000, European Medicines Agency, 2001, European Medicines Agency, 2006, Kleiber et al., 2017). In 2007 European legislation was introduced to ensure that medicinal products used with CYP are subject to high quality research and improve the information available on their use (Permanand et al., 2007). These legislative changes have encouraged the pharmaceutical industry to study medicines in CYP (European Parliament and the Council of the European Union, 2006, Kleiber et al., 2017). As a result there are more clinical trials in paediatric patients (Kemper et al., 2011). However, there are concerns that these reflect those that bring the greatest financial benefit to the pharmaceutical industry (Choonara and Sammons, 2014) and there is still substantial discrepancy between paediatric burden of disease and the volume of clinical trials taking place (Bourgeois et al., 2012).

1.2 Paediatric Intensive Care setting

The situation is compounded by critical illness. The proportion of off-label or unlicensed drugs can reach up to 70% in Paediatric Intensive Care Units (PIC) (Turner et al., 1996) and 90% in Neonatal Intensive Care (Conroy et al., 1999) putting them at greater risk of possible treatment failure or toxicity. In addition, critically ill children can receive up to 18.5 different drugs during a PIC admission (median 14) with up to 129 drug administration episodes (median 58) (McDonnell et al., 2009) putting them at risk of an adverse drug

reaction or interaction. Pasquali et al (2008) highlight that multiple off label prescribing is common with 48% (of 31, 432 paediatric patients who had cardiovascular disease) receiving two or more cardiovascular drugs off label and 31% receiving three or more medications. Organ dysfunction is also common in such groups with 50% of patients in PIC exhibiting two or more dysfunctional organ systems (Leteurtre et al., 2006). This may modify drug absorption, metabolism, elimination further, altering the expected response to standard doses and increase the risk of toxicity and other adverse drug events (Kearns et al., 2003a, Thakkar et al., 2017). In PIC patients at a local level, around 90% of patients experience single organ failure, requiring invasive ventilation (PICANet, 2016), and many also require additional complex interventions such as Extra Corporeal Membranous Oxygenation (ECMO) and renal replacement therapies. ECMO is known to affect pharmacokinetic profiles in critically ill patients and guidance for dosing in these patients is challenging (Mousavi et al., 2011, Thakkar et al., 2017). It is therefore imperative that the number of trials in children continues to grow in order to create a child-specific evidence base which is methodologically strong and relevant (Klassen et al., 2009). Research is needed to improve care in urgent and emergency situations but should only be undertaken in these situations if absolutely necessary and if non-emergency research will not resolve the uncertainties (Modi et al., 2014).

1.3 Pharmacokinetics: what is it and why is it important?

The scientific study of medicines in children is known as paediatric clinical pharmacology (Hoppu, 2008). Pharmacokinetics is the scientific study of how the body handles a medicine and describes the movement of drugs through the body over time and addresses the absorption, distribution, metabolism and elimination from the body (Thomson, 2000,

Kanneh, 2002a, Kanneh, 2002b, Vermeulen et al., 2017). The scientific information generated from pharmacokinetic studies and studies of drug toxicity ensure that medicines are used rationally in children (Choonara and Sammons, 2014). Pharmacokinetic studies have traditionally required a rigid, experimental design with serial multiple blood sampling, usually taken according to a rigidly timed and structured protocol within a relatively small patient population (Royal College Paedatrics and Child Health, 2004, Patel et al., 2010, Thomson and Elliott, 2011). Although this conventional approach leads to an accurate and precise estimation of PK parameters its feasibility and interpretation are limited by several factors, including difficulties in recruitment, patient selection and blood loss (Wurthwein et al., 2005).

1.4 Challenges of conducting pharmacokinetic research

1.4.1 Consent

Conducting clinical trials in the Paediatric Intensive Care (PIC) environment is recognised as having very specific challenges (Kanthimathinathan and Scholefield, 2014). Parents need to make informed decisions about participation at times of uncertainty and when experiencing extreme anxiety (Kleiber et al., 2015). Historically there has been a reluctance to recruit 'vulnerable' patients to research studies, fearing of adding to the burden families already experience (Michelson et al., 2006). In addition Research Ethics Committees have also expressed concerns about involvement of children deemed vulnerable (Angell et al., 2010). Clinical trials conducted within life threatening situations are impeded by the difficulty of obtaining traditional informed consent during clinical stabilisation. A number of studies have explored the feasibility and acceptability of methods where consent is gained *after* the investigatory treatment has been given (Morris et al., 2004, Morris et al., 2006, Gamble et

al., 2012). In the UK his has been termed 'deferred consent' or research without prior consent (Woolfall et al., 2015). This approach was legalised in the United Kingdom in 2008 and was utilised in a large Randomised Controlled Trial (RCT) of Central Venous Catheters in 14 PICs across England and Wales (the CATCH trial) (Gilbert et al., 2016). Deferred consent was obtained for 84% of families who were approached, indicating that deferred consent was an effective strategy for recruitment within the high stress environment of PIC (Harron et al., 2015). Further studies indicate that parents support the approach in a paediatric emergency situation such as Status Epilepticus (Chamberlain et al., 2009, Woolfall et al., 2014) and this could extend to other situations where urgent action is required, such as obtaining PK levels of a medication administered within an emergency. Further work is required to explore the perspective of CYP and parents within this specific area.

1.4.2 Sampling from peripheral vascular access

Many PK study protocols refer to the use of peripheral vascular access (cannulas) as the source for blood sampling. Not only can initial placement of cannulas in children and young people be extremely challenging (Latour, 2000), but obtaining blood samples by 'bleeding back' cannulas on an on-going basis can be challenging due to distress and the requirement to cooperate (Becht and Anderson, 1996, Hands et al., 2010, Thomson and Elliott., 2011). In addition, many protocols make specifications that there must be a second cannula specifically for sampling. Protocols can stipulate placement in an extremity and in some cases require placement in a contra-lateral limb to where an intravenous medication is being administered, to avoid 'downstream contamination' (Kauffman and Kearns, 1992). These rigid requirements are challenging for CYP, particularly when studies can request 14 samples within 24 hours (Su et al., 2010, Kukulka et al., 2014).

1.4.3 Pain

Children's adverse reactions to medical situations has long been recognised (Prugh et al., 1953). Undergoing invasive or painful medical procedures causes distress and anxiety (Duff, 2003, Dlugos et al., 2005, Hands et al., 2010) and there is also recognition that children can become distressed by equipment or the setting or even because of memories of pain from earlier experiences (Von Baeyer et al., 2004). Procedures involving needles seem to be particularly difficult for young children (French et al., 1994) and a traumatic experience can cause fear and anxiety for future procedures in hospital (Gilboy and Hollywood, 2009).

1.4.4 Topical anaesthetic agents

Using topical anaesthetic agents is the gold standard for children who require venepuncture for reducing pain (Cordoni and Cordoni, 2001). Use of EMLA cream has been shown to significantly decrease pain scores in adults during venepuncture compared with placebo (Hijazi et al., 2009) and paediatrics (Hopkins et al., 1988) and topical refrigerant spray has also been shown to be effective in paediatric patients for venepuncture (Schlieve and Miloro, 2015). However despite the known negative effects of anxiety on the perception of pain (Kolk et al., 1999), analgesia is not always used for venepuncture in children (Hands et al., 2010).

1.4.5 Alternative strategies

The use of play therapy and other distraction techniques to reduce the distress associated with venepuncture has also been described within the published literature (French et al., 1994, McCarthy and Kleiber, 2006). Rates of use vary, with techniques used in only 23-28% of venepuncture attempts (Ellis et al., 2004, Hands et al., 2010) . There are suggestions that preparing CYP for a procedure is related to less child distress (Kolk et al., 1999), however, providing information and preparing CYP is often dependent on parent attitudes. If parents

have a favourable attitude towards healthcare, they provide better preparation (Rodriguez et al., 2012). In addition, the attitude of clinical staff can heavily influence the conduct of a procedure (Ellis et al., 2004). Analgesia, distraction, play, parental presence and better information about procedures all influence CYP and parent views in clinical practice. It is likely that these will also impact on the approach and discussion about research with both CYP and parents. Further work is required to determine the optimum combination for research participation.

1.4.6 Use of central vascular access or arterial lines

To reduce additional painful procedures there is the possibility of using central venous lines (CVL) or arterial lines (indwelling lines) to access samples (European Medicines Agency, 2001, Thomson and Elliott, 2011). Traditionally many studies have not accepted this approach, fearing contamination of samples. A study comparing readings from paired peripheral and central venous line (CVL) samples for Cyclosporin levels found that there was no significant difference in the concentration by sampling site. This meant samples obtained from the CVL were reliable and therefore children did not require additional painful venepuncture (Senner et al., 2005). Using existing lines is relatively quick and simple allowing timely collection and minimal disruption to patients (Salazar, 2003). However, there are issues associated with staff competence and expertise to access central venous and arterial lines (Altamimi et al., 2016). In addition, placement of arterial lines usually requires close observation in an area such as PIC (Way, 2000).

Using analgesia, distraction, play, parental presence, better information about procedures and the use of clinically indicated vascular access devices to obtain samples (and avoid pain) will impact on the approach and discussion about research with both CYP and parents.

Further research is required to determine the optimal combination for research participation.

1.4.7 Anaemia and infection risk

There are significant concerns about the impact of blood sampling on children for clinical indications. Historically PK studies involved the collection of numerous blood samples (as many as 15-20) *in addition* to clinically indicated blood tests (Choonara and Sammons, 2014) This creates concerns for clinical staff about reduction in Haemoglobin from participation in a clinical pharmacology study as well as increased infection risk factors associated with the frequency with which a central line may be accessed (Cole et al., 2006). There are discrepancies in recommendations for acceptable blood volumes for PK research. Blood sampling practice varies in published studies from 1ml/kg of total blood volume (Allegaert et al., 2008), 1.5 ml/kg if above 12 months of age (Kearns et al., 2000), 1.8ml/kg (Allegaert et al., 2007), no more than 1% of circulating volume (Turanlahti et al., 2004), less than 3% of circulating volume (Reed et al., 1996, Haig et al., 2001), less than 5% of the estimated circulating volume (Ala-Kokko et al., 2005) to a total of 70mls/patient (Agertoft et al., 1999). This lack of concordance creates confusion for researchers and for those who regulate research from an ethical perspective (Koren et al., 1988, Sammons et al., 2007b). These potential extra risk factors associated with PK research participation may impact on clinical staff, parents and children's decision making about study enrolment.

In summary, there are indications from the literature that consent, pain, sampling, anaemia and infection might all cause issues to PK research studies. Pharmacokinetic studies have tended to involve serial sampling of multiple bloods, usually taken according to a rigidly timed and structured protocol within a relatively small patient population (Royal College

Paedatrics and Child Health, 2004, Patel et al., 2010, Thomson and Elliott, 2011). It would therefore seem likely that recruitment to such studies would be challenging (Wurthwein et al., 2005) and researchers need to think creatively to find solutions.

1.5 Overcoming challenges

Within the PK literature researchers have identified methods which could potentially contribute to overcoming challenges associated with PK trial conduct.

1.5.1 Population based pharmacokinetic modelling

Population based pharmacokinetic modelling to support clinical trials can reduce the number of samples required from each individual within a population by increasing the overall population size (Batchelor and Marriott, 2013). The advantage for paediatric trials is that fewer samples are required per individual (a sparse data approach) and there can be flexibility in the sampling times (Vermeulen et al., 2017, Barker et al., 2018). Overall this means there is less disruption to the patient and their clinical care (Bartelink et al., 2006, Ahsman et al 2010, Thomson and Elliott, 2011). The population PK approach is generally used in patients being given the drug therapeutically and therefore poses fewer ethical issues about the exposure of children to experimental medicines (Hawcutt and Smyth, 2008). This approach is increasingly evident in the literature (Tod et al., 2008, Barker et al., 2018) and would seem to overcome some of the issues associated with painful additional procedures. There are also examples of patients being randomised to different sampling 'windows' with a specific regime. For example group 1 has samples at 1 hour and 4 hours and group 2 has samples at 30 minutes and 2 hours (Simpson et al., 2006). This method is felt to be valuable, provided that the actual sample time is accurately recorded (Thomson and Elliott, 2011). However, with participants providing fewer samples, there are

implications if samples are not obtained. It is not known whether using principles of population PK modelling would affect recruitment or how patients and their families make sense of this approach.

1.5.2 Combining research and clinical care

Studies which are conducted in the context of routine clinical care are much more likely to be ethically justifiable and scientifically desirable (Thomson and Elliott, 2011). It therefore follows that arranging for blood samples to be taken for research and for routine purposes at the same time is a useful starting point for a study (Wintermeyer et al., 1997, European Medicines Agency, 2001, Nielsen et al., 2009, Hawcutt and Smyth, 2008). Opportunistic sampling is not widely described but could contribute to a population PK approach. However, if the blood is difficult to draw clinical requirements should take priority, which could potentially lead to the loss of research data. Another approach would be to use samples taken for routine clinical monitoring (Saez-Llorens et al., 2009a) so there are no 'additional' samples required or to utilise blood left over after other tests have been conducted; opportunistic sampling or 'scavenged samples' (Leroux et al., 2015). An alternative would be that additional samples, samples taken specifically to measure PK for research purposes could be made available for clinical management. This method does not appear to be widely practiced, however, it would be interesting to know the perspective of service users and health professionals on this strategy and whether this would be a useful addition to clinical management.

1.5.3 Innovations in sampling

Traditionally the preferred fluid for obtaining repeated assessments of drug concentration has been blood. However in paediatric patients ethical, physiological and sometimes

practical limitations influence the availability of biological samples required for pharmacokinetic studies (Kauffman and Kearns, 1992). Drug assay concentrations from non-blood samples can be used in some circumstances in order to establish pharmacokinetic information. Approaches such as the use of saliva may offer the possibility of replacing blood levels of certain drugs (Wells et al., 2009). In a study examining parental attitudes to DNA studies, after using residual dried blood spots from newborn screening (which had already been taken), buccal cell collection was parents' next preferred method (Jenkins et al., 2009). Whole blood spotted onto filter paper- dried blood samples- is a well-established technique for collecting and storing blood in screening newborns for genetic and metabolic disorders (Carpenter and Wiley, 2002). However some researchers have utilised the technique for drug monitoring in vulnerable groups such as neonates (Patel et al., 2013). The main advantage is that samples are micro-volume, stable at room temperature for relatively long periods and they present less of a biohazard for transportation (Patel et al., 2010). Given the concerns that exist over sampling volumes in vulnerable populations, techniques which support micro-sampling, with low volumes of blood are increasingly popular.

Urine has often been included as a potential alternative with studies comparing the results obtained with plasma concentrations. However, unless a patient has a medically indicated indwelling bladder catheter the collection of timed, quantitative urine specimens could be problematic in infants and young children (Walker, 2000).

In summary, there are emerging methods to reduce painful procedures, reduce the sampling demands and attempts to reduce the invasiveness of PK trials. The next stage is to assess the acceptability of these methods to potential participants and their families.

1.6 Situation in 2009

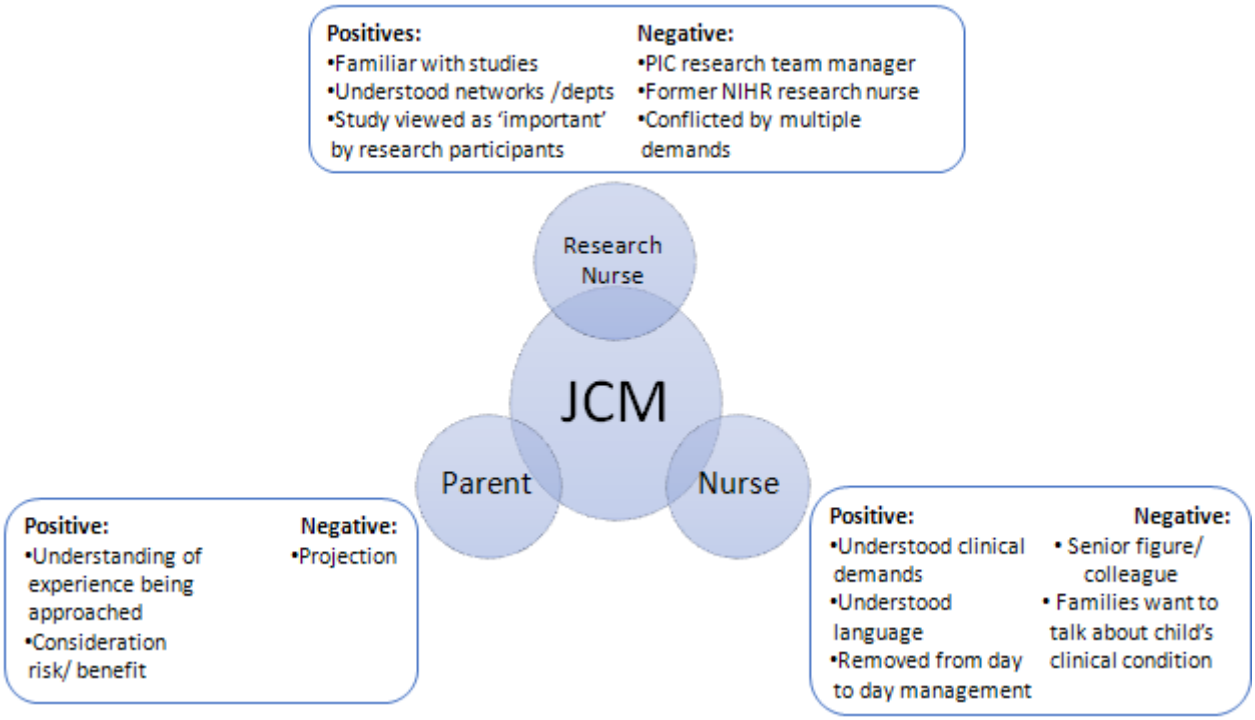
At the time when the PhD funding was awarded for the project research in children of any age represented only around 1 in 10 of all applications to the National Research Ethics Service, of which less than 10% were trials of an investigational medicinal product (Modi and McIntosh, 2011). Protecting children in research seemed to have translated to excluding children from clinical trials (Knox and Burkhart, 2007). Across Europe there was a recognition that children were being neglected and that medicines used for children should be scientifically evaluated for both efficacy and toxicity (Hoppu, 2008). European regulations had been established requiring pharmaceutical companies to conduct and share information regarding trials in paediatric populations, including encouraging the provision of licensing information for older off-patent drugs as well as newly developed medicines (Sutcliffe and Wong, 2006, Modi and McIntosh, 2011). Medicine research in children was recognised to be a priority area with the creation of the National Institute for Health Research (NIHR) Medicines for Children Research Network (MCRN) (Saint-Raymond and Seigneuret, 2005, Duffin, 2007, Sammons and Choonara, 2007, Choonara and Bauchner, 2008). The award was made for the PhD, which came to be termed PRESCRIBE; Pharmacokinetic RESearch in CRitically Ill children: facilitating the BEst design to review the design of PK research. The focus was on research with acutely ill CYP, therefore the project is reflective of academic-led protocols and research, conducted within the NHS. As industry-sponsored studies can take place within paediatric NHS organisations, study participants

could, and did, reflect on these. Industry work conducted within Clinical Research Organisations was not included (unless participants' had specific experience of these and chose to reflect on these experiences).

1.7 Reflexivity

Qualitative research stresses the importance of reflexivity, whereby the researchers recognise they have a social identity and background that has an impact on the research process. Reflexivity will reveal the researchers' own particular position and the factors which may have influenced interpretation should be made clear (Carter and Goodacre, 2012). Adopting a review of the researcher (JCM) there were three key aspects which could influence the conduct of the research. The influence of the researcher as a nurse (Registered Nurse since 1997), research nurse; formerly with the NIHR clinical research network (West Midlands) and at the time of the research the PIC nursing research team manager, and the influence of being a parent (from 2012). *Figure 1* below summarises the key factors associated with each role and the positive and negative influence of each. To promote a self-critical stance to the research the researcher had regular supervision, during which the influences of all these components were reviewed. A summary of the influence of these throughout the project is included in Chapter 9 (see *9.3 Reflexivity*).

Figure 1: reflexivity on JCM as researcher, research nurse and parent



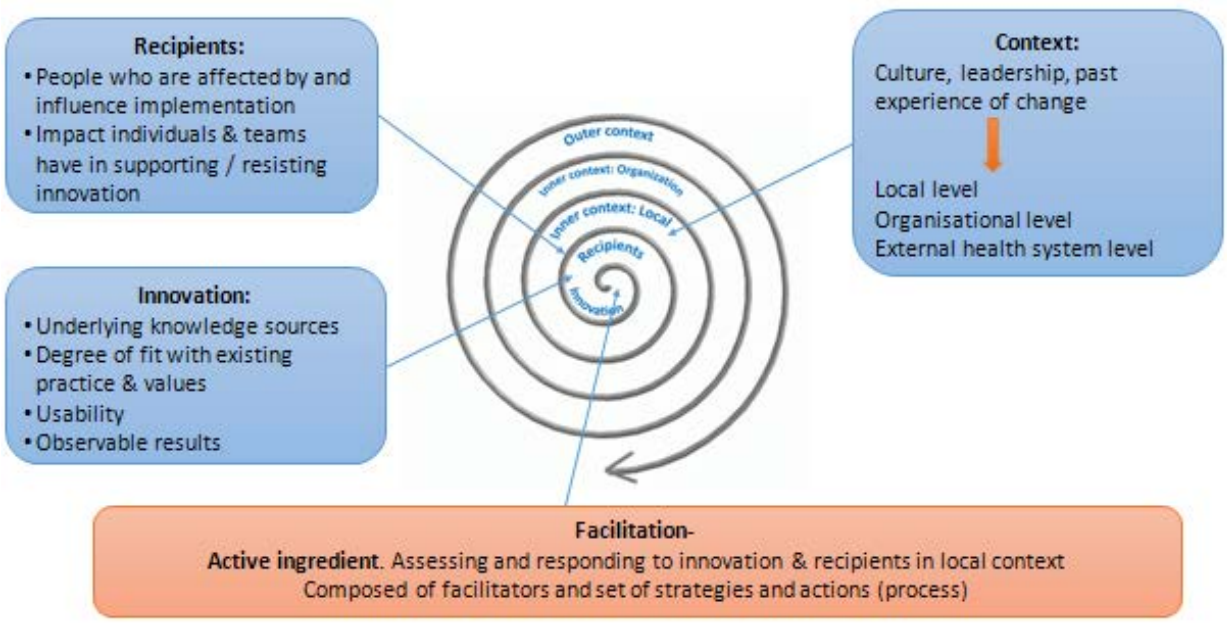
1.8 Evidence based medicine and implementation science

Evidence based practice (EBP) is the conscientious, explicit and judicious use of current best evidence in making decisions about the health care of patients (Sackett et al., 1996). The evidence based 'movement' has been widely adopted across health and social care as a strategy for providing the highest quality of healthcare (Craig and Stevens, 2012). However there is evidence that research has a disappointing impact on practice (Nutley et al., 2000). Research cannot change outcomes unless health services and healthcare professionals adopt the findings into practice (Eccles and Mittman, 2006). The basis of PRESCRIBE is about understanding factors affecting the conduct of PK research however the output is guidelines to assist future researchers in PK study conduct. How the work would fit into the context of care and be of practical utility for staff was therefore fundamental to the project. The literature surrounding EBP was therefore reviewed and identified the relevance of implementation Science- associated with the issue specifically of implementing research

evidence into practice (Ferlie et al., 2000, Grol and Grimshaw, 2003, Eccles and Mittman, 2006). Implementation models are commonly used to describe and guide the process of translating research into practice and within these determinant frameworks are those that seek to identify barriers or enablers that are important to address (Nilsen, 2015, Birken et al., 2017). The most widely used of these approaches is PARIHS (Promoting Action on Research Implementation in Health Services) (Kitson et al., 1998a, Kitson et al., 1998b) which emphasises the importance of 'evidence', 'context' and 'facilitators'. This was the model initially felt to be the most appropriate.

The scoping review of the literature would provide insight into the facilitators and barriers that have been identified with published PK studies ('evidence'). The qualitative enquiry would provide insight into lay and professional views and attitudes toward PK research through targeted stakeholder groups in the context of both ward areas and PIC ('context') and from all of this the support ('facilitation') needed to help people change their attitudes, habits, ways of thinking and working identified. However it became apparent for the purposes of PRESCRIBE the model did not give sufficient attention to the stakeholders; the people both affected by and who influence potential implementation (Thompson, 2012, Rycroft-Malone et al., 2013). Nor did it help with differentiation between issues at the local level and those within the wider organisation. In recognition of this the i-PARIHS approach which has been developed from PARIHS was adopted. Please see *Figure 2* below.

Figure 2: I-PARIHS key components (Harvey and Kitson,2016)



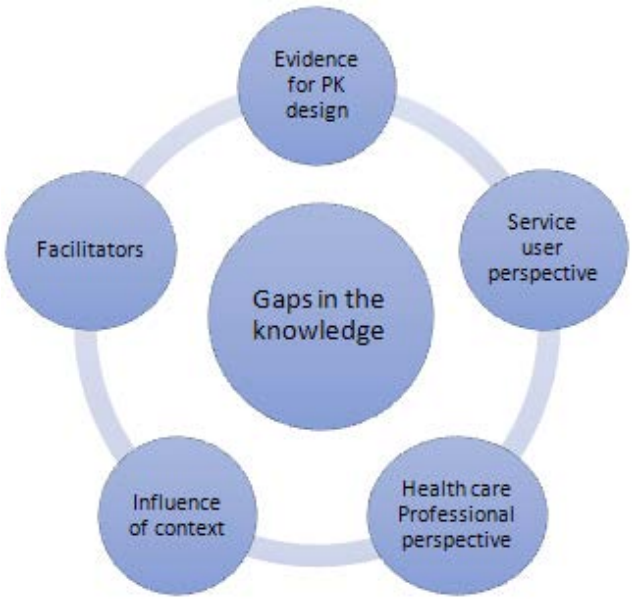
I-PARIHS (Integrated-PARIHS framework) builds on the original approach, developing the concepts of evidence to 'innovation', context and facilitation and introducing a new construct of 'recipient' (Harvey and Kitson, 2016). Facilitation has developed to become an active element assessing, aligning and integrating the other three constructs. Successful implementation is defined in terms of the achievement of implementation / project goals and results from the facilitation of an innovation with the recipients in their local context. The process is represented as a spiral which starts with a focus on the innovation and recipients before moving out to consider the context at local and then the wider level. Although the model had not been widely implemented at the time it seemed to be appropriate to the implementation endeavour.

1.9 Gaps in the knowledge

From the literature, it is clear there are a number of gaps in the knowledge. These have been identified as: evidence for PK study design, service user perspective, health care

professionals' perspectives and the impact of context, particularly in the face of critical illness and facilitators (see *Figure 3* below).

Figure 3: gaps in the knowledge



1.9.1 PhD strategy

Based on the gaps in the knowledge a strategy was devised to gather an evidence base. The chapter structure is outlined below in *Table 1*. This highlights the aim of each aspect, the underpinning theory and how each addressed a gap in the knowledge.

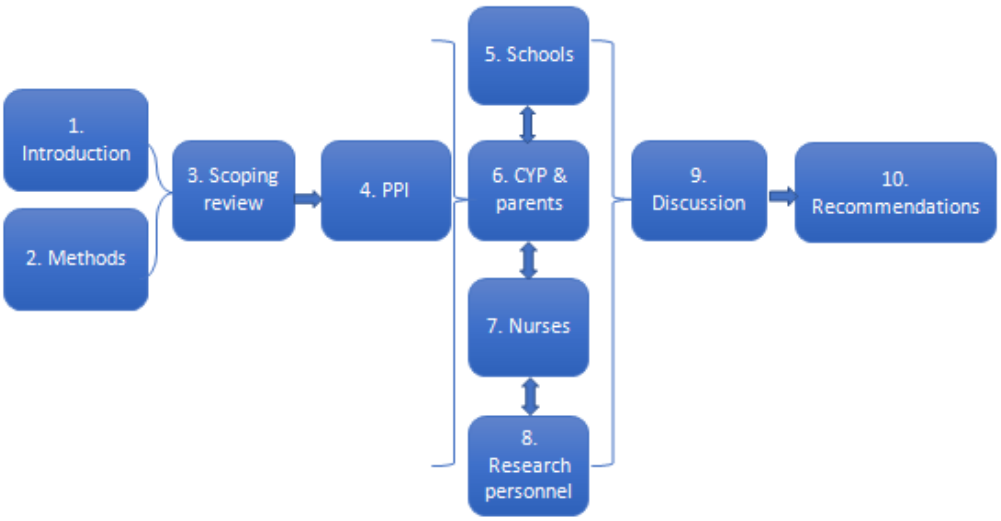
Table 1: summary of PhD structure and content

Study	Aims	Underpinning theory	Gap in knowledge
Scoping review	Identify strategies that: I. facilitate recruitment II. barriers to conduct of PK studies	Deductive approach: scope existing knowledge	• Evidence for PK study design • Influence of context • Facilitation
Patient & Public Involvement (PPI)	Identify: i. stakeholders ii. recruitment methods iii. methodology iv. develop interview schedule	Inductive approach: collecting information to inform future research	Service user perspective

Study	Aims	Underpinning theory	Gap in knowledge
Quantitative research: • **Children & Young People (CYP)**	Identify stakeholder: I. attitudes II. views of barriers III. views of facilitators & relationships	Deductive approach: Formulating hypothesis and proposing relationships between variables	• Evidence for PK study design • Service user's perspective • Facilitation
Qualitative descriptive research with: • **Children & Young People (CYP)** • **Parents** • **Nurses** • **Research personnel**	Understand stakeholder: i. attitudes ii. views of barriers iii. views of facilitators	Inductive approach: collecting information to develop recommendations	• Evidence for PK study design • Service user's perspective • Health Care professionals' perspective • Influence of context • Facilitation
Recommendations for PK study conduct	Develop recommendations for future PK studies protocol and study conduct	Deductive: strategy informed by previous work	Evidence for PK study design

As identified earlier, the work was conducted sequentially with chapters 4 and 5 informing the subsequent ones (6-8) (see *Figure 4)*. Chapters 6-8 were then conducted concurrently in an interactive manner with similarities and differences compared and contrasted in chapter 9. Recommendations were generated and are reported in chapter 10.

Figure 4: outline of PhD chapters.



Chapter 2: Methodology chapter

2.1 Introduction

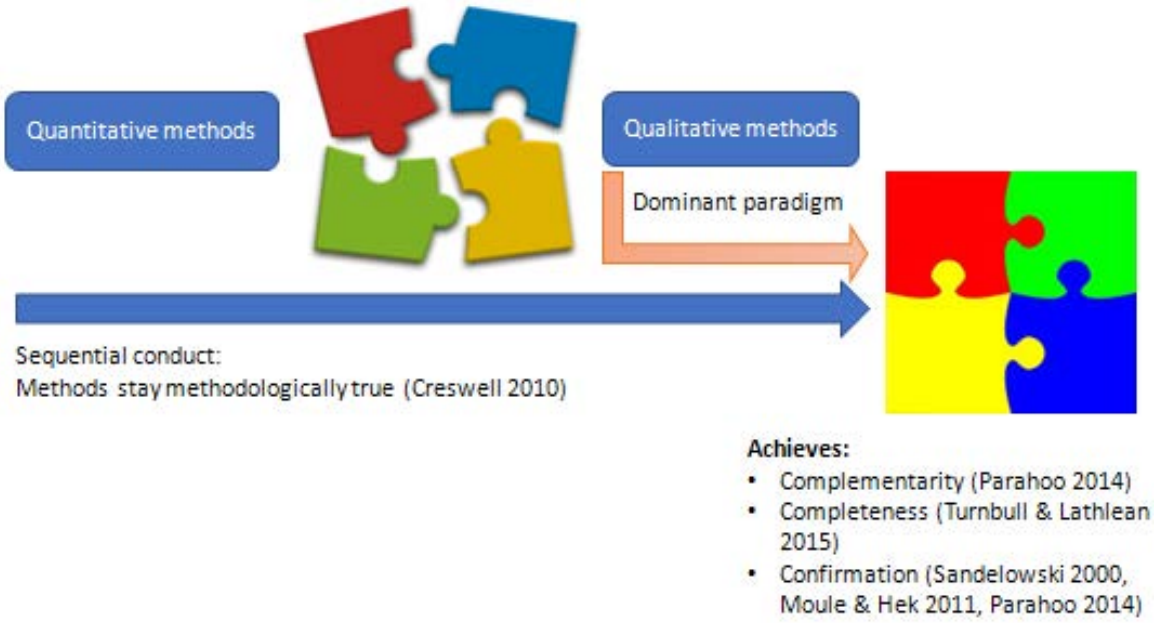
Within chapter 2 the aims of the study, the approaches taken, the rationale behind these approaches, the research methods and the analysis are presented. All methods for chapters 4-8 are detailed together within this chapter to avoid repetition.

2.2 Paradigms and approach

The purpose of this PhD work was to make sense and explore meaning, rather than to test theory or explore cause and effect relationships. The researcher and the project therefore sit within an interpretivist paradigm, and the belief that the social world is actively constructed by human beings who are continuously involved in making sense of or interpreting the social environment (Parahoo, 2014). Considering the gaps in the knowledge, it was necessary to develop a multi-method programme to address the research questions Both qualitative and quantitative methods have been used throughout the PhD, an approach referred to as 'mixed methods'. Mixed methods have been described as research in which the investigator collects and analyses data, and draws inferences using both qualitative and quantitative approaches and methods in a single study or a programme of inquiry (Tashakkori & Creswell, 2007). Critics of mixed methods approaches argue that mixing methods is not feasible because the two paradigms are incommensurate (Turnbull and Lathlean, 2015). However, those who support the approach as feasible believe this is possible as long as one approach is dominant, with the theoretical 'drive' drawn from this paradigm (Morse, 2003, Morse and Niehus, 2009). PRESCRIBE overall has adopted a partially mixed, sequential, dominant status, mixed methods typology (Leech and Onwuegbuzie, 2009). The dominant approach and therefore the 'theoretical drive' (Morse, 2003) is a

qualitative approach. Parahoo (2014) compares this application of different methods as similar to the construction of a whole, complete picture by fitting jigsaw pieces together (see *Figure 5* below).

Figure 5: mixed methods approach to PRESCRIBE



The quantitative and qualitative components were conducted independently and sequentially, which allowed the different components to remain true to their own paradigm and methodology requirements (Cresswell, 2010), without descending into a 'qualitative quagmire' (Barbour, 1998). The use of different methods allowed the researcher to study the same phenomenon for confirmability or corroboration in an on-going iterative process (Sandelowski, 2000a, Moule and Hek, 2011, Parahoo, 2014). Overall adopting this approach using both sequential and concurrent methods (for the qualitative components) allowed the researcher to achieve complementarity, completeness and confirmation (Sandelowski, 2000a, Moule and Hek, 2011, Turnbull and Lathlean, 2015) .

The merits of a number of qualitative approaches were reviewed. Ethnography focuses on culture which was an aspect of interest, however the emphasis on anthropology and world view (Polit and Beck, 2010) was not felt to be appropriate. Action research emphasises change, rather than understanding (Dew, 2007) which was also not felt to be the most appropriate method. Phenomenology, with an emphasis on understanding an individual's lived experiences (Ritchie, 2003) was felt to be more appropriate for PRESCRIBE. However, with outcomes from the study wanting to address the implementation of evidence into practice this was felt to be the wrong emphasis. A qualitative descriptive (QD) approach was therefore adopted. This approach is regarded as useful for researchers wanting to know the who, what and where of events, and for gaining insights from participants where a phenomenon is poorly understood (Sandelowski, 2000b). Key features of QD design are outlined below in *Table 2*.

Table 2: qualitative description design issues[1]

Aspect	Approach
Philosophy	Pragmatic approach
Reflexivity	Important for the researcher to describe their disciplinary affiliation and what brought them to the question
Sampling	Purposeful. Maximum variation sampling is especially pertinent
Data collection	Minimum-moderately structured interviews with individuals / focus groups Researchers are interested in the who, what, where and why of the experience
Analysis	Qualitative content analysis, can be supplemented with descriptive statistics Stay close to the data- low level interpretation
Outcomes	Straight description of the data organised in a way that 'fits' the data. Results are firmly connected to the data
Rigour	Clear audit trail, consideration of saturation, triangulation

[1] Caelli et al., 2003, Sandelowski, 2000b, Neergaard et al., 2009

In summary, often the phenomenon at the heart of qualitative research has not been previously investigated and as Chapter One has demonstrated there are a number of gaps in the knowledge surrounding the conduct of PK research. A mixed methods approach, utilising a qualitative descriptive method, which stays close to the data and recognises the value of quantitizing qualitative data to add emphasis and provide a measure of scale (Tashakkori and Teddlie, 1998) was therefore adopted.

2.3 Research aims and objectives

2.3.1 Research aim

The overall aim of the thesis is to determine the best design features and methods for conducting pharmacokinetic research with children and young people (CYP) who are critically ill.

2.3.2 Research objectives

Objectives for Chapters 3-10 are listed in *Table 3* below.

Table 3: objectives for Chapters 3-8

Chapter	Objectives
Chapter 3	To conduct a scoping literature review of paediatric pharmacokinetic research studies and identify and quantify: **a**. Strategies that improve recruitment to paediatric pharmacokinetic research **b.** Barriers to recruitment or retention to paediatric pharmacokinetic research
Chapter 4	1. To develop the research protocol prior to Research Ethics Committee (REC) submission in consultation with members of the public, to include: a) Identification of the stakeholders[1] in paediatric PK research studies (potential participants) b) Identification of recruitment strategies for future participants (recruitment methods) c) Identification of the methods to conduct research with future participants (methodology) d) Identification of questions to utilise with future participants (interview

	schedule) [1]stakeholder refers to persons, groups or organisations that are considered to have a significant influence on the success of a project and need to be taken into account by leaders, managers and front-line staff (Bryson, 2004). **2**. To develop participant information sheet (PIS) and consent / assent forms.
Chapter 5	Utilising quantitative methods: **a.** Determine the attitudes of a lay paediatric population towards paediatric PK studies **b.** Identify what a lay paediatric population perceive to be barriers or problematic about the conduct of paediatric PK research studies **c.** Identify what lay paediatric population identify to be enabling or facilitating the conduct of PK research studies
Chapter 6-8	Utilising qualitative methods: **a.** Determine the attitudes of participants towards paediatric PK studies **b.** Identify what participants perceive as a barrier or problematic about the conduct of paediatric PK research studies **c.** Identify what participants identify as enabling or facilitating the conduct of PK research studies
Chapter 9	Compare and contrast lay population, service user and health care professionals' attitudes and perceptions of barriers and facilitators to the conduct of PK research
Chapter 10	Using evidence generated from chapters 3-8 develop guidelines for pharmacokinetic study design and conduct for future research studies, with a focus on the context of CYP who are critically ill.

2.4 Research design

The overall research design and methodologies are summarised in *Table 4* below.

Table 4: summary of research design for all PhD chapters

Work stream	Sampling	Method	Pilot	Approvals	Data management	Analysis	Rigour
Scoping review (SR) (Chapter 3)	Systematic against set criteria	Scoping review method	Preliminary searches	X	Endnote	Reviewed against inclusion criteria. Results themed.	Adherence to SR method
PPI (Chapter 4)	Purposive	Training Focus group (FG)	N/A	X	• Intelligent transcription • Anonymised	Thematic analysis	• 2 separate sessions • Member checking • Summarising and checking within sessions
School CYP (chapter 5)	Convenience	Education Vignette Questionnaire	10 CYP (Yr 10) 5 CYP (Yr 10-11)	REC not required √ Head teacher	• Locked office, secure corridor (for paper questionnaires) • Anonymised • Electronic database (NHS server)	SPSS Thematic analysis (free text)	• Conducted with variety of schools, variety of locations • Content validated with experts
CYP (Chapter 6)	Purposive	Vignette FG /Interviews	Vignette developed from SR Piloted within school children sessions	√ REC √ R&D	• Recording device stored in NHS facilities (locked corridor) • Audio-files transferred to NHS server (and deleted from recording device) • Intelligent transcription • Anonymised • Imported into NVivo 11	Review of transcript (generated from audio-recording) • Coding- structural & magnitude coding • Mind maps • Qualitative Content Analysis • Framework analysis • Descriptive statistics (excel)	• Concurrent analysis within groups and between groups • Researcher triangulation • 'True to participant voice' • Triangulation with quantitative statistics
Parents (Chapter 6)		Vignette Interviews					
Nurses (Chapter 7)		Vignette FG/ interview		√ R&D			
Research Nurses (Chapter 8)		Vignette FG/ Interviews					
R&D staff (Chapter 8)		Vignette FG/ Interviews					

2.5 Sampling

2.5.1 Sample population

The sample populations for each work stream were developed through consultation and engagement with the public (Patient and Public Involvement (PPI). This work is detailed in more depth in chapter 4. The sample populations are defined below.

2.5.1.1 School children (lay children)

The key group identified within the PPI work was children and young people: with two groups- those with hospital experience and those without (a 'lay' group). They felt the best way to find and engage with those naïve or less experienced with the hospital setting was to recruit CYP in the school setting. PPI participants felt participants should be years 9-13 (aged 13-18years). This age was justified as they felt CYP needed to be able to understand the concepts of ill-health, decision-making and understand why research is conducted. Year 9 was felt to be the year when these topics start to be addressed within science and Personal, Social, Health Education (PHSE) lessons. Screening and recruitment took place through a number of methods; schools already engaged with the National Institute for Child Health, schools engaged with Birmingham Children's Hospital and schools engaged with University of Birmingham through enrichment events (see *Table 5)*. A convenience sampling strategy was utilised, recruiting all CYP who met the inclusion criteria who attended schools which agreed to participate during the period of study. The pupils were felt to be representative of the wider year as there was no chance to self-select or volunteer. Although this method offers the highest risk of introducing bias (LoBiondo-Wood and Haber, 2006), random sampling techniques were not feasible due to the challenges of finding sufficient schools to engage with.

Table 5: summary of inclusion and exclusion criteria: CYP (school setting)

<table>
<tr><th colspan="2">School children</th></tr>
<tr><td>Inclusion criteria
• Head teacher approval for CYP to participate in the study
• Parents given option to decline their child's participation
• CYP in years 9-13
• No restrictions on health status, medication usage or previous hospital experience
• CYP consented to participate with questionnaire through 'tick' on paper questionnaire</td><td>Exclusion criteria
• Head Teacher declined school participation
• CYP whose parent declined their participation in the session.
• CYP in school years 8 and below and 19years and over.
• CYP declined consent to questionnaire (verbally or on questionnaire)</td></tr>
<tr><td colspan="2">Screening methods:
1. Identification of school through those already engaged with National Institute for Health Research (NIHR) Clinical Research Networks (3 schools)
2. Schools engaged with Birmingham Children's Hospital to attend an outreach event (1 school)
3. West Midlands schools attending University of Birmingham (UOB) Enrichment Events with School of Pharmacy (6 schools)
Screening, approach & recruitment
1. NIHR contacts
• Schools contacted (Head Teacher) through email introduction from NIHR Clinical Research Network
• If head teacher agreed to participation then class teachers identified and contacted by the researcher
• Science and PHSE sessions were targeted (following PPI suggestions). Dates negotiated with individual teacher.
• Teacher sent out Participant Information Sheet (PIS) to parents of CYP in the class. PIS informed them of their right to decline consent for their child to participate in the session. The school would facilitate attendance at an alternative class.
• All CYP within the class (Year 9-13) were included (unless parents declined)
• Contact with schools, liaison with teachers, session conduct, distribution of questionnaire (all JCM)
• CYP consented through 'tick' to indicate consent at the start of the questionnaire
2. Birmingham Children's Hospital
• School that participated in an outreach event at Birmingham Children's Hospital.</td></tr>
</table>

- All CYP who attended outreach events eligible for inclusion
- Liaison with school, session conduct, distribution of questionnaires (JCM)
- CYP consented through 'tick' to indicate consent at the start of the questionnaire

3. **University of Birmingham**

- One-day enrichment events scheduled by School of Pharmacy, UOB.
- Sessions for PRESCRIBE timetabled within this day.
- All CYP (years 9-13) who attended sessions eligible for inclusion
- Liaison with schools (UOB), session conduct, distribution of questionnaires (JCM)
- CYP consented through 'tick' to indicate consent at the start of the questionnaire

2.5.1.2 Children and young people (CYP) and parents within the hospital setting

CYP and parents with experience of the hospital setting were identified as a key group to interview. These groups were refined further to CYP aged over 8years of age (as advised by the PPI work) and parents of any age of child, with experience of PIC and / or experience of participation in clinical trials. Purposive sampling was used to screen and recruit CYP / parents who met one or both of these criteria. In purposive sampling decisions are made about which criteria are used for selection early on in the research design stages, shaped by hypotheses that the research might want to explore or gaps in the knowledge about the study population (Parahoo, 2014). These strategies were outlined at the outset within the research protocol and Research Ethics Committee (REC) submission and in keeping with recommendations, sampling was done as rigorously and systematically as possible (Proctor et al., 2010). Screening records were kept and maintained by the research nurses who worked on Paediatric Intensive Care (PIC) and screened PIC on a daily basis for multiple

studies, and the researcher, who maintained screening records for Wellcome Trust Clinical Research Facility (WTCRF). Inclusion and exclusion criteria are defined below (see *Table 6 below*).

Table 6: summary of inclusion and exclusion criteria: CYP and parents stakeholders

CYP	Parents
Inclusion criteria • CYP who attend or have attended BCH aged 8-18 years[1] • Attendance at outpatients' department, research clinic in Wellcome Trust Clinical Research Facility (WTCRF) or inpatient on any ward at Birmingham Children's Hospital (BCH) including PIC[2] • Siblings or relative of a child who has attended hospital eligible[3] • Members of CYP advisory groups who did not participate with PPI work could be invited to participate[4] • Parents were involved to assess CYP cognitive ability to participate.	**Inclusion criteria** • Parents or guardians of children aged 0-18years who attend or have attended BCH. • One or both parents invited to participate, either at the same time or separately • Attendance at outpatients, WTCRF or inpatient stay on any ward at BCH.
[1] The age of 8 for CYP with 'experience' of health care was recommended by PPI consultation work and Hall et al (2001) [2] There are low numbers of PIC admissions aged 8 years +. Local data suggested <14% were 8 years and the majority of PIC bed days nationally are required by children <1 year of age (57%) (PICANet National Report, 2015). [3]PPI participants felt siblings could offer an insight into research. This was supported by a paper which included siblings in discussions surrounding participation of their brother or sister in research (Snethen and Broome, 2001). [4] There were two groups at a local level- NIHR Young Persons Advisory Group (YPAG) (focus on medicines research) and a BCH YPAG (non-research focus). Members who had not participated were invited to participate in the qualitative work.	

CYP	Parents
Exclusion criteria • CYP who could not speak English • CYP with insufficient cognitive abilities to participate in focus group discussion (determined through sensitive discussions with parents/ clinicians) • Members of the YPAG who had previously participated in PPI activity for the study in 2013 were excluded (n=6)	**Exclusion criteria** • Parents / carers who could not speak English • Parents who do not have parental responsibility for their child or where there were shared care arrangements with social services.
Screening methods: • PIC admissions (screening assisted by PIC research team) • WTCRF attendance (screening assisted by WTCRF research team) • Referral from Family Liaison team on PIC • Referral from BCH Specialist Nurses • Referral from BCH Patient and Public Experience lead	
Screening, approach & recruitment • PIC research team screened all PIC admissions and discharges for eligible CYP/ Parents. Discussed study, provided with PIS, asked for completion of contact details. Information supplied to the researcher. • WTCRF research team screened specific studies for eligible CYP / parents. Provided researcher with clinic dates of eligible patients. • Researcher allowed two mornings / afternoons a week to screen / follow up on those identified through research support • Arranged interview / focus group at participant's convenience • Liaised with other sources for referrals, provide them with PIS and follow up. • Consent / assent obtained by the researcher (JCM)	

2.5.1.3 Nursing staff

The sampling frame was defined as clinical nurses who worked at Birmingham Children's Hospital, 2013-2014, Bands 5-8, in Paediatric Intensive Care (PIC) and High Dependency (HD) ward areas. Purposive sampling was conducted to sample nurses with experience of intensive or high dependency care in ward areas. See *Table 7* below.

Table 7: summary of inclusion and exclusion criteria: nursing staff

Clinical Nurses	
Inclusion criteria • Clinical Nurses working at BCH, Band 5-8. • Employed in intensive or high dependency ward areas- PIC, Liver, Cardiac wards. • No limitations placed on experience or length of employment in research. • Can communicate in English	**Exclusion criteria** • Unregistered practitioners Band 4 and below
Screening methods • Ward Managers • Education links for wards (where they existed) • Advanced Nurse Practitioner (ANP) • Snowballing- approached by two clinical areas	
Screening, approach and recruitment • Purposive sampling to recruit nurses with an email invitation and Participant Information Sheet (PIS) sent via Ward Managers. First approach- April 2013 (PIC), September 2013 (Wards 8, 11,12), Second approach November 2013 (all wards) • Education links for wards (where role existed) contacted.	

Clinical Nurses
• Two further wards contacted- Medical Day Care (MDC) and Burns Ward after initiation by individual staff members • Advanced Nurse Practitioner (ANP) lead facilitated arrangement of focus group with ANP's • Participants asked to contact JCM directly to arrange focus group attendance • Responses could be made by email, answer phone or post indicating their availability and preferences • Focus groups were timed to occur alongside staff training / meetings • Facilities were booked to ensure private, quiet and confidential surroundings. • Discussed study with participants, provided with PIS, given opportunity to ask questions. • Consent taken by JCM • All focus groups and interviews conducted by JCM • If a participant was unable to attend the focus group, arranged interview at participant's convenience

2.5.1.4 Clinical Research staff and Managers

The sampling frame was identified as those with research expertise- research staff (within NHS organisations) and those reflecting a hospital management perspective on the conduct of research- 'hospital managers' (see *Table 8* below). Research staff were staff Band 5-8 employed at Birmingham Children's Hospital, 2013-2014, in a department specific research role or within the National Institute for Health Research (NIHR) Research Network role. Additional study sites were added in order to add different research perspectives, responding to emerging themes. The NIHR Clinical Research Network South West team covered a large number of vaccine studies, which involved additional painful procedures and blood sampling, so it was therefore felt to be useful to add their perspective (following REC and local R&D approvals). The inclusion of neonates within research appeared to be an area of concern across participant groups,

therefore the research team at Birmingham Women's Hospital NHS Trust (following additional approvals) were purposively invited to participate. It was initially difficult to define who represented the management perspective towards research, but after consultation with the R&D Manager and Deputy Chief Nurse the R&D committee were felt to be the best representatives. The sampling frame was therefore members of the BCH R&D panel who reviewed the approval and conduct of all research at BCH.

Table 8: summary of inclusion & exclusion factors: research staff

Clinical Research Staff	Hospital Managers
Inclusion criteria • Clinical Research Staff working at BCH 2013-2014, Band 5-8. • No limitations placed on experience or length of employment in research, including experience outside of the NHS setting with Pharmaceutical companies • No limitations on professional background • National Institute for Health Research (NIHR) Medicines for Children Research Network (MCRN) West Midlands research team[1]. • Extended to staff within NIHR MCRN South West team[2] • Staff within the NIHR networks could be based throughout the West Midlands or the South West, although their base and place of employment was BCH and United Hospitals Bristol (UHB). • Birmingham Women's Hospital (BWH) neonatal research team. A team of research nurses who cover studies within the neonatal unit.	**Inclusion criteria** • Member of BCH Research and Development Facilitation Committee (responsible for approval of all research at the BCH NHS Trust)[3]. • Attendance at monthly meeting on the day of the planned focus group.

Clinical Research Staff	Hospital Managers
[1] Now termed NIHR Clinical Research Network (West Midlands) [2]Now termed NIHR Clinical Research Network (South West) [3]The panel includes representatives from the NIHR Clinical Research Network, R&D manager, R&D finance, pharmacy, labs and radiology	
Exclusion criteria Staff with job descriptions 'data managers', 'research administrators' or 'trials managers'; roles which did not have direct influence over trial design or patient contact within clinical trials.	**Exclusion criteria** No exclusions criteria on the basis of professional background. R&D panel at BWH not eligible[4]
[4]BWH and BCH are now one Foundation Trust (2017). At the time of the research these were separate organisations with separate R&D approvals processes. Approval was only granted to include BCH R&D teams	
Screening, approach and recruitment • Purposive sampling to recruit NIHR Clinical Research Network staff with an email invitation and Participant Information Sheet (PIS) sent via Managers. • Screened total staffing records (provided by managers) to review response rates. • Focus groups were timed to occur alongside staff training / meetings • Facilities were booked to ensure private, quiet and confidential surroundings. • Discussed study with participants, provided with PIS, given opportunity to ask questions. • Consent taken by JCM • All focus groups and interviews conducted by JCM • If a participant was unable to attend the focus group, **a**rranged interview at participant's convenience	

2.5.2 Sample size

Recommendations for sample size in the majority of qualitative studies generally follow the concept of reaching saturation; that any new data does not shed any further light on the issues under investigation (Glaser and Strauss, 1967). Data saturation however is difficult to define and there is little practical guidance for researchers on actual sampling sizes. A sample size of 20 was considered to be appropriate, as little 'new' information is felt to emerge after this (Green and Thorogood, 2009, Mason, 2010, Snelgrove and James, 2011), although there was flexibility in this, recognising that there was uncertainty about the influence of different ward contexts on reaching data saturation (Glaser and Strauss, 1967). Within paediatric qualitative studies similar numbers appear to have been consulted; 17 CYP and 22 parents (Farrington et al., 2016), 25 CYP (Luchtenberg et al., 2015) and 23 caregivers and 29 CYP (Patterson et al., 2011, Patterson et al., 2015). Within PRESCRIBE the notion of 20 participants per group was outlined. Once no 'new' information was being yielded, saturation would be deemed to have occurred (Parahoo, 2014). A single site approach was felt to be appropriate for most participant groups. The exception was the Clinical Research Nurses where further sites were added in light of emerging themes.

2.6 Approvals

Ethical approval is not required for the active involvement element of the research, where people are involved in planning or advising on research, nor are researchers required to obtain written informed consent from patients and members of the public (National Research Ethics Service and INVOLVE, 2009, Boote et al., 2010). REC approval was therefore not obtained for the PPI activity but Good Clinical Practice (GCP) recommendations in dealing with CYP and parents were adhered to (National Institute for Health Research, 2016a). Research Ethics Committee (REC) approval was also not required for the work

within schools as it was classed as an 'educational intervention'. The University Research Ethics Committee and Sponsor (University of Birmingham) were satisfied with this. No formal consent process by CYP and parents was therefore required. Research involving NHS patients and their families does however require the approval of a REC (Gelling, 2015, Lacey, 2015) as well as approval by research governance from the site where the research will be conducted (Department of Health, 2005). See *Table 9* below.

Table 9: summary of approvals for PRESCRIBE project

Approval	Reference number and date
NHS REC approval: NRES Committee South Central-Oxford A	Ref No. 12/SC/0051 Approval date: 18.01.2012. Extension applied for until 31.12.2015.
University approval: University of Birmingham	Reference Number: ERN_11-1275
Sponsorship: University of Birmingham	Ref RG_11-208 Approval date: 05.04.2012
Research & Development approval: Birmingham Children's Hospital NHS Foundation Trust Birmingham Women's Hospital NHS Trust United Hospitals Bristol (UHB)	 Reference number: 12/SC/0051 Approval date: 05.04.12 Ref Number: 62998 Approval date:20.09.2013 Ref Number: CH/2013/4416 Approval date: 24.10.2013

Research Ethics Committee approval is not required for research conducted with NHS staff (Gelling, 2015) (from 01.09.2011). However there is still the requirement for Research and Development (R&D) approval to ensure that research governance requirements are fulfilled (Moule and Goodman, 2009). R&D approval was applied for and obtained on 05.04.12. In addition, local R&D approval was sought for University Hospital Bristol (UHB) the host organisation for NIHR Clinical Research Network South West and for Birmingham Women's Hospital (BWH).

2.7 Data collection methods

2.7.1 Vignette

A vignette was used throughout the work streams to prompt people to respond to a hypothetical specific situation (Arthur and Nazroo, 2003). The same one, modified to the knowledge and orientation of the participants, was used throughout interviews and focus groups, to promote continuity (Wilson and While, 1998). This also facilitated comparison between participants and participant groups. Although vignettes provide more context than questions alone they can be criticised for being uni-dimensional and cannot predict how people might react in real life situation (Moule and Goodman, 2009). However, this was felt to be the best method available to use within the time and circumstances available. The vignette was developed to represent a 'typical' PK study protocol, based on information gained after reading over 1000 paediatric PK publications for the scoping review. Key features identified were samples were usually blood, most commonly from peripheral vascular access (from a cannula specifically inserted as 'extra' for sampling purposes) and most sampling took place within the first 24 hours, with approximately 8 in total. These features were incorporated within the vignette (see *Appendix 1*). Variables were then changed to elicit information about respondents' perceptions and opinions (Polit and Beck, 2010), for example the type of vascular access was changed to a central venous line or the context was changed from a ward area to PIC. Vignettes were utilised for all qualitative work and within all methods. The vignette was developed from feedback from the pilot for the questionnaire (15 CYP). The vignette was the core component of introductory material (for all participant groups, including CYP and parents). This material provided information about what pharmacokinetics was and why measurements were required, before introducing the vignette. This material was displayed electronically or on a paper handout (dependent on the location and facilities available). Provision of this type of information is

vital for participants who undertake a PPI role (Telford et al., 2004, Staniszewska and Denegri, 2013, Bagley et al., 2016). Training needs to be relevant, interesting, but also age and developmentally appropriate (Kirby, 2004, INVOLVE, 2016a, INVOLVE, 2016b). PPI participants suggested that similar material should be provided at the start of focus groups and interviews to provide background to the work and clarity on the purpose of the study. The background information was therefore developed through feedback from the PPI group (6 CYP) and piloted with 5 CYP from a school Young Person Advisory Group. Minor amendments to this were conducted to ensure clarity of message.

2.7.2 Interview schedule

The interview schedule was recognised to be a key element to ensure the central research question was addressed, while also allowing new and interesting responses to be explored (Tod, 2010). Development of the schedule was therefore recognised to be a crucial aspect of the PPI work to ensure not only the clarity of questions for participants, but also the sequencing of questions was appropriate. Sensitivity was also required, particularly when discussing potentially emotive topics (Polit and Beck, 2010), such as conducting research with CYP who are not expected to survive. The schedule was essentially the same for all participant groups to permit exploration of the same issues and examine similarities and differences, but the language was modified and oriented to the particular position of the respondents (Glaser and Strauss, 1967). (Please see *Appendix 2* for the interview schedule utilised with CYP). Prompt questions were identified for each group to encourage participants if they lost their thread or to re-engage them with the interview (Tod, 2010). Efforts were made to follow question wording precisely and in the same order. However, if a participant appeared to find an aspect of conversation distressing and indicated they wished to move on, or appeared not to understand an area of questioning, the researcher moved

the schedule along, recognising the responsibility of the researcher to make the interview a pleasant and satisfying experience (Polit and Beck, 2010). The interview schedule was reviewed by the supervision team, by two Registered Children's Nurses and by two Patient and Public Involvement experts. It was piloted with two participants and found to require no amendments, therefore these respondents are included within the analysis.

2.7.3 Questionnaire

Questionnaires are self-report forms that are useful to elicit information about beliefs, attitudes or opinions (Burns and Grove 2011). A questionnaire refers to when respondents complete the instrument themselves, usually in a paper format (Polit and Beck, 2010). This method was selected for the work conducted with school children because a structured, standardised, pre-determined approach with the same questions in the same order asked of all respondents was required (Parahoo, 2014). Sessions were time-restricted and an approach was required which could ensure that the work was conductible within the available time. Researchers are advised that wherever possible, an existing questionnaire with established reliability and validity should be utilised (Jones and Rattray, 2010). However, one did not exist exploring attitudes towards PK studies therefore a questionnaire was developed with questions which could be asked within the subsequent qualitative work, to allow comparison and facilitate triangulation. Demographic data were gathered at the beginning of the questionnaire to prompt respondents to report on their medication use, health status and hospital experience. Likert scales were used to measure attitudes with a range of 5 pre-coded options, ranging from strongly agree to strongly disagree (Hassan et al., 2015). Multiple choice formats were used to allow respondents to select the one (or more) options that best applied to them (Parahoo, 2014). The questionnaire was composed of pre-dominantly closed-ended or fixed-alternative questions. This approach is

more efficient and is also useful with groups who may not feel confident answering more open-ended questions (Polit and Beck, 2010). The disadvantage of this approach is that omission of potentially important alternatives might occur or answers might be relatively superficial. Participants are also deprived of the opportunity to express their own opinions or to elaborate on responses (Polit and Beck, 2010). In order to overcome this free text options were offered in each domain to allow participants to expand upon answers (Jones and Rattray, 2010). The questionnaire was completed at the end of an interactive discussion which introduced the concept of research with children, children's medicines and pharmacokinetics, a similar strategy to prepare and set the scene to a study with CYP about unlicensed medications (Mukattash et al., 2012). The questionnaire was distributed in paper form as computers were not widely available and the researcher was available to assist with answering questions, which is associated with a higher response rate (Moule and Goodman, 2009). The PIS emphasised the voluntary nature of completion of the questionnaire. In order to reduce pressure upon students as the work was conducted in classroom settings, the questionnaire began with a simple consent statement students 'ticked'. This meant they had a discrete method of declining participation if they did not want to participate and allowed response rates to be monitored. The questionnaire was piloted with 10 CYP from a year 10 Science class in January 2012. Feedback predominantly focused on the layout, lack of pictures and terminology. Following modification this was then re-piloted with a small group of CYP (5) within a school. No further modifications were required to the questionnaire.

2.7.4 Focus groups

Focus groups were the preferred method for the patient and public engagement work, as well as the qualitative work with CYP, parents, nurses and research staff. The benefit to

focus groups is the emphasis on moderated group discussion; with research participants enabled to exchange, discuss, agree or disagree about opinions, attitudes and experiences (Kitzinger 1995, Parahoo 2007). They are felt to be less intimidating and time intensive than one to one interviewing and encourage attempts to identify, describe, analyse and resolve key issues (Kitzinger, 1994, Ritchie, 2003, Goodman and Evans, 2010). The size of a focus group varies typically from between 5- 12 members (Goodman and Evans, 2010) (Krueger and Casey, 2000). There are challenges for all groups in availability and a pragmatic approach was adopted, recognising that sessions would be run with fewer if changes to availability occurred. All focus groups were set up and moderated by the researcher (JCM) with field notes taken by an independent research nurse (where available) following training by JCM. New purpose built, accessible, research facilities, separate from clinical care areas were booked for sessions (Marlowe, 2008, Bell, 2009) and service user participants were offered refreshments and travel costs (Edmunds, 1999, Marlowe, 2008). Consent was taken immediately prior to the session commencing by JCM for all participants to indicate they were satisfied with the information they had received and were happy for sessions to be audio-recorded and transcribed. For CYP, informed consent was taken from parents with assent from CYP, (or consent directly from the CYP if they were aged over 16years). Please see *Appendix 3* for a full list of PIS and consent and assent forms developed for PRESCRIBE. The PIS provided to parents of CYP who were eligible for participation and for CYP and the consent and assent forms are included (*Appendix 3a-e*). Clear 'ground rules' for the focus group were established at the outset and the sessions were facilitated to try to ensure all participants were given the opportunity to contribute (Rennie et al., 2002, Shaha et al., 2011). Sessions were planned for relatively homogenous participants, for example a group of children with the same rare disease, in the same clinical trial. Homogenous groups are

generally preferable to ensure free discussion and enable cross-group comparisons (Morgan, 1997, Goodman and Evans, 2010). Using pre-existing groups or groups of people who are already meeting for another purpose, is also useful to ensure participants are relaxed and facilitates participation. This also reduces the challenge of bringing people together at the same time (Kitzinger, 1994, Parahoo, 2014).

2.7.5 Interviews

Interviews are known to have a number of advantages: higher response rates, allowing clarification, permitting more in-depth questioning and probing and allowing the interviewer to judge the respondents' level of understanding (Polit and Beck, 2010). This approach is particularly useful when little is known about an area. However, this method is extremely time-consuming and does not facilitate the stimulation of discussion through participant interaction as happens within a focus group (Kitzinger, 1994). The decision was therefore made to promote focus groups as the predominant method, with one to one interviews offered to participants (CYP, nurses and research staff) in the event of unavailability for focus group attendance or personal preference. This allowed us to engage with 'hard to reach' groups; people who would be reluctant or unable to participate using other methods (Tod, 2010). This proved essential for the successful recruitment of parents. The same interview schedule was utilised for all participants (focus group or interview) to allow comparison between group participants. These sessions were also audio recorded and transcribed following consent and assent.

2.8 Data Analysis

2.8.1 Data management

The questionnaires were transported to and stored in a locked office in line with Data Protection Act requirements (Data Protection Act, 1998). These were then entered into a

database manually, given a unique study number to ensure participant anonymity before importing into SPSS for statistical analysis.

The recorded audio files from PPI work and qualitative interviews / focus groups were transferred to a secure NHS password protected computer and deleted from the recording device. They were transcribed and all identifying information was deleted with a unique study number allocated. These were then imported into NVivo for qualitative analysis.

2.8.2 Analysis- questionnaires

Data yielded from the questionnaires was predominantly nominal and ordinal. Nominal variables were compared using Fisher's exact test, an alternative to the Chi-square test, which gives exact p-values, rather than relying on an approximation (McDonald, 2014). The ordinal variables did not meet the assumptions for parametric analyses, since they followed skewed distributions and so non-parametric analyses were used (Hicks, 1999). Where ordinal variables were compared between two groups, Mann Whitney U tests were used (Freeman and Walters, 2010), with Kruskal-Wallis tests used for comparisons between three or more groups (Hicks, 1999). For all of the analyses, the null hypotheses were that there was no difference between the groups being compared. Two-sided p-values were reported, as the direction of any effect had not been pre-specified (Hicks, 1999), for example, it would be of interest if male school children were either more or less likely to agree with PK research on children than females. Using a two-tailed hypothesis was judged as appropriate because there was little background information to inform specific predictions. Throughout the analysis, a critical p-value of 0.05 was used, meaning that any p-values that were <0.05 were deemed to be indicative of a significant effect (Freeman and Walters, 2010).

Where a significant difference was detected in a comparison of more than two groups, post-hoc tests were performed, in order to identify which of the individual pairs of groups the observed differences occurred between. For significant Kruskal-Wallis tests, this was achieved using Dunn's test (also known as Bonferroni adjustment). This allowed comparison between each pair of groups separately with the p-values Bonferroni corrected (Dinno, 2015). Bonferroni correction is appropriate when there are a relatively small number of comparisons being made and only a small number are likely to be significant (McDonald, 2014).

Some of the questions were not answered by all respondents, resulting in missing data, although the numbers of missing values were very small. These cases were treated as 'missing at random', whereby it was assumed that those respondents that did not answer questions were not a biased sample of the cohort as a whole (Carpenter and Kenwood, 2017). Respondents with missing data were therefore excluded from the analyses relating to the questions where answers were not recorded, but remained in the analyses for the other questions for which data were available (McCormick et al., 2015). All analyses were performed using IBM SPSS 22.

2.8.3 Analysis- interviews and focus groups

2.8.3.1 Transcription

Transcription has been described as central to the process of analysis. It refers to the process of reproducing spoken words into written text and it represents what the researcher and the transcriptionist preserve from the taped speech (Maclean et al., 2004). The decision was made to use 'intelligent transcription' rather than 'verbatim transcription' which removes the conventions of dialogue e.g. pauses which can be difficult to read (Gale et al., 2013). Although verbatim transcription has been cited as central to the reliability,

validity and veracity of qualitative data collection, drawbacks to this approach reflect the time and human resources required to capture these nuances (Wellard and Mckenna, 2001). Researchers must focus on their research objectives and make appropriate decisions about the level of transcription required (Bird, 2005, Oliver et al., 2005, Davidson, 2009) and the decision was made that intelligent transcription was sufficient. The first 5 transcripts were conducted by the lead researcher JCM and following this were outsourced to a transcription service with a signed confidentiality agreement in place. As recommended within the literature (Maclean et al., 2004, Halcomb and Davidson, 2006, Davidson, 2009), clear guidelines were provided to clarify the documentation of emotion, inaudible sections, medical terminology and conversation fillers. Following transcription there was a phase of data cleansing where the transcripts were reviewed alongside the audio and the authenticity verified.

2.8.3.2 Field notes

In studies which involve using recording equipment, field notes provide an opportunity to record what researchers see and hear, their thoughts about the dynamic of the encounter, ideas for inclusion in later fieldwork and issues that may be relevant at the analytical stage (Arthur and Nazroo, 2003). Field notes were recorded during focus groups by an independent research nurse (where available) and by JCM after the sessions. This enabled clarification of participant's speech, correct attribution to participants and notes on emotion and non-verbal behaviours helped clarify meaning. Notes were not made during 1:1 interviews due to feasibility, but were made as soon after as possible by JCM.

2.8.3.3 Coding

Coding is an interpretive act which enables the researcher to organise and group similarly coded data into categories and make sense of patterns (Saldana, 2013). This is an iterative

process and recoding occurs with a more attuned perspective so eventually some first cycle codes will be subsumed by other codes, relabelled or dropped altogether. Abbott (2004) likens the process to decorating a room: you try it, step back, move a few things, step back again and so on. A structural coding approach was utilised; a basic but focused, content-based approach to coding (Saldana, 2013). This is consistent with qualitative content analysis of staying close to the description of the data (Sandelowski, 2000b, Neergaard et al., 2009). Structural coding is particularly appropriate for studies with multiple participants as it can act as a labelling indexing device. This allows researchers to quickly access data likely to be relevant from a large data set and serves as a categorisation technique (Namey et al., 2008). Quantitative applications are then possible and data can be quantified with code frequencies explored to identify which themes, ideas or domains were common, and which rarely occurred (Tashakkori and Teddlie, 1998). A second coding strategy of magnitude coding was utilised, coding for attitudes in a simple manner as 'positive', 'negative' and occasionally 'neutral' codes. Magnitudinal codes add adjectival or statistical texture to qualitative data and assist with mixed methods or quantitative studies by indicating intensity or frequency as well as weight and importance (Saldana, 2013).

2.8.3.4 Qualitative content analysis

Qualitative analysis is based on a common set of principles: transcribing the interviews, immersing oneself in the data to gain detailed insights into the phenomena, developing a data coding system and linking codes or units of data to form categories or themes that lead to the development of theory (Morse and Richards, 2002). The analysis method was qualitative content analysis. Analysis focused on coding interview material, looking for commonalities and differences in the data (Miles and Huberman, 1994) and developing themes. A theme captures something important about the data in relation to the research

question and represents some level of patterned response or meaning within the data set (Braun and Clarke, 2006, Fereday and Muir-Cochrane, 2006). This method also supports the supplementation of qualitative analysis with quasi-statistical analysis, summarising some data with descriptive statistics (Neergaard et al., 2009). This quantifying can help to confirm suspicions and can assure readers that researchers' assumptions are valid (Tashakkori and Teddlie, 1998). The objectives of PRESCRIBE were to understand more about the barriers and facilitators to conducting PK research. Providing an idea of the magnitude of these through quantifying was felt would avoid too much weight being given to dramatic or vivid accounts or too little weight to disconfirming cases (Sandelowski, 2001).

2.8.3.5 Framework analysis

The Framework Method for the management and analysis of qualitative data is a matrix-based analytical method which facilitates systematic, rigorous and transparent data management. It allows the analyst to move back and forth between the raw data and cross-link initial categories (Ritchie et al., 2003, Gale et al., 2013). While in depth analysis of themes can take place across the whole data set, the views of each research participant remain connected to other aspects of their account so that the context of the individual's view is not lost. Data can be compared and contrasted across cases as well as within cases and the method is recognised as particularly useful for managing large data sets. A series of main themes emerge, subdivided by a succession of related subtopics. This method enables the researcher to explore the data in depth whilst simultaneously maintaining an effective and transparent audit trail, enhancing the rigour of the analytical processes (Ritchie, 2003, Smith and Firth, 2011).

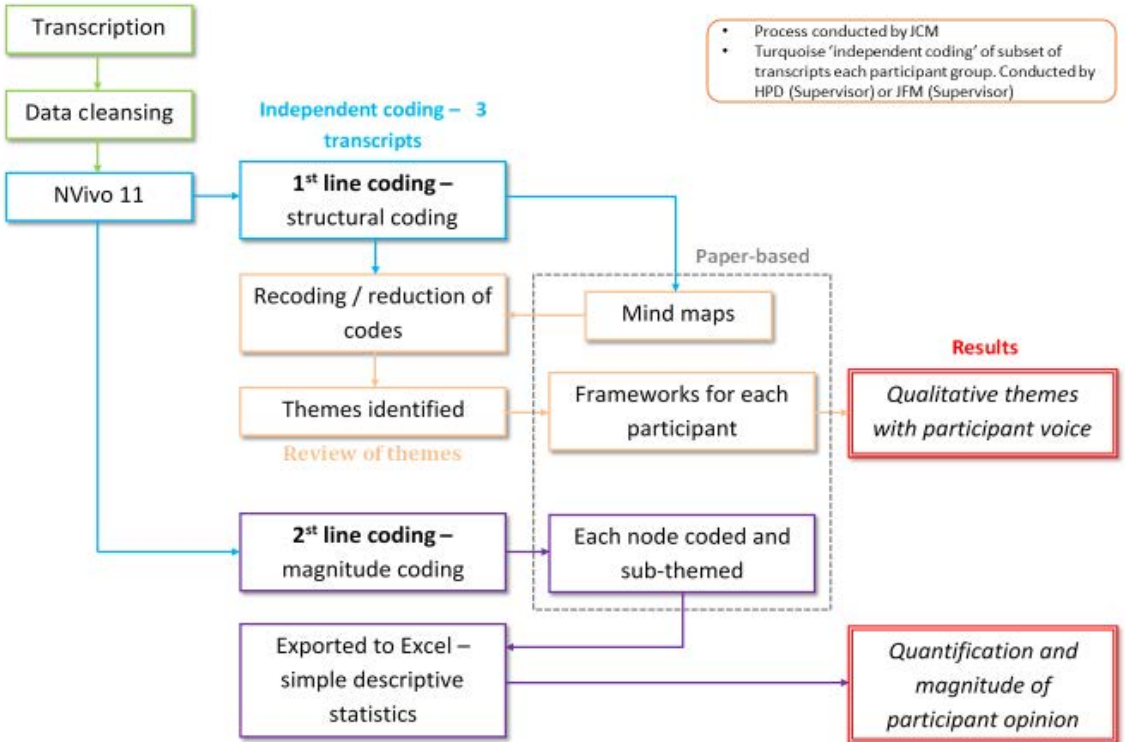
This method was felt to be appropriate due to the large volume of planned interviews and focus groups and the ability to compare and contrast cases. This also assisted with

quantifying the data (Tashakkori and Teddlie, 1998) and confirming the impression of an association (Sandelowski, 2000a, Sandelowski, 2001).

2.8.4 Analysis approach

One of the criticisms of qualitative approaches is the lack of transparency in how the researchers have made sense of their data. In order to minimise this, the approach to analysis is detailed, with supplementary material available in *Appendix 4*. The process as a whole is summarised in *Figure 6.*

Figure 6: summary of the qualitative analysis process



Initial coding was conducted within NVivo software. These were reviewed; combined, subsumed in other codes or removed. Mind maps were used to make sense of nodes and themes were identified. Some nodes fitted into more than one category, so there was some fluidity about their placement. However, all nodes could be categorised into these seven themes and there were no outliers. Each theme and the sub-codes were then used to create a template framework for each participant group and each individual's responses

were plotted. The matrix served as a means to ensure key messages were kept and the essence of each individual's responses was represented. This was particularly helpful as a number of these participants were interviewed in focus groups and it was sometimes difficult to separate individual voices. This also served as a reminder where there were particularly useful quotes.

Within NVivo 2nd line magnitude coding then took place where there were attitudinal responses to different codes. Each code had notes made (paper records), to detail how many positive / negative comments there were and the number of people making these comments. All comments were traceable to the individuals. These figures were plotted in excel to provide quantitative data on the magnitude of participant opinion. All reporting featured both the number of comments and the number of participants to avoid misuse of the numbers and the influence of one person dominating a topic. The number of participants was not reported alone as participants could comment both positively and negatively and it was felt the volume of comments was a stronger measure of magnitude.

2.9 Ethical considerations

2.9.1 CYP and parents

There were deemed to be minimal potential risks of undertaking this study for all participants. The main concern was the possibility that taking part might raise distressing memories of events for CYP or parents from previous hospital attendances. In recognition of this the PIS highlighted key topics such as blood sampling and medicines would be discussed in order that potential participants could make an informed decision about participation. Participants were reassured throughout the process that they could stop the interview at any time and the PIS outlined that they had a week after the interview to withdraw consent. If this happened the interview would be deleted. It was recognised that

parents could become distressed reflecting on their past situation or there was the potential to identify a family in need of additional support. In recognition of this a support algorithm was devised which identified sources of support CYP and parents could be referred to (see *Appendix 5*).

2.9.2 Clinical and research staff

The PIS highlighted to staff that if they made a disclosure or a statement which highlighted unsafe practice or practices which contravened hospital policy this information would be shared with their line manager. In all other situations anonymity and confidentiality were assured. If any distress was experienced a referral to on site psychology services would be made recognising the right of all participant groups to have their wellbeing protected (Department of Health, 2005, National Institute for Health Research, 2016a).

2.10 Reliability and validity- quantitative work

Reliability is defined as the extent to which results are consistent over time and an accurate representation of the total population under study (Golafshani, 2003). Within this is the concept of the repeatability of a questionnaire; that it will measure what it is supposed to measure in a consistent manner (Jones and Rattray, 2010). Test-retest reliability can be done to check consistency over time, however this was not feasible within the time constraints of classroom sessions or outreach events. Reliability was therefore addressed through alternate-form test or equivalence, where small changes of wording assess the consistency of participants' responses (Parahoo, 2014). Validity refers to whether the questionnaire measures what it is supposed to measure and if it measures it correctly and accurately (Golafshani, 2003). Through two sets of pilot tests with CYP, the items appeared relevant and unambiguous and all respondents appeared to follow the instructions in the same way. Face validity was therefore felt to have been addressed. Content validity was

enhanced through consultation with pharmacology experts outside of the research team to ensure that the questionnaire items represented the constructs to be measured (Polit and Beck, 2010). Although the group discussion sessions with CYP in schools were not audio recorded, field notes were recorded (Watson et al., 2010). These served to summarise observations from the session, including overall attitude from the group, feelings of understanding and comprehension and any areas of confusion. These reflections helped to promote criterion related validity, the extent to which a measure relates to an outcome. Key features are summarised in *Table 10* below.

Table 10: summary of methods used to ensure reliability and validity of the research

Term	Method employed	Strategy
Reliability- questionnaire	Alternate form re-retest	Concepts checked within questionnaire
Validity- questionnaire	Face validity Content validity Criterion validity	Pilot test / re-test 15 CYP Review ability answer questionnaire Expert consultation Triangulation with field notes
Dependability- qualitative methods	Audit trail Triangulation Reflexivity	Coding trail Sources, methods, coding methods, researcher Researcher position and perspective disclosed
Trustworthiness- qualitative methods	Thick description Member checking Triangulation Negative case analysis	Participant voice, methods and analysis In interview checking Sources, methods, coding methods, researcher Review of examples which do not 'fit'

2.11 Dependability and trustworthiness- qualitative research

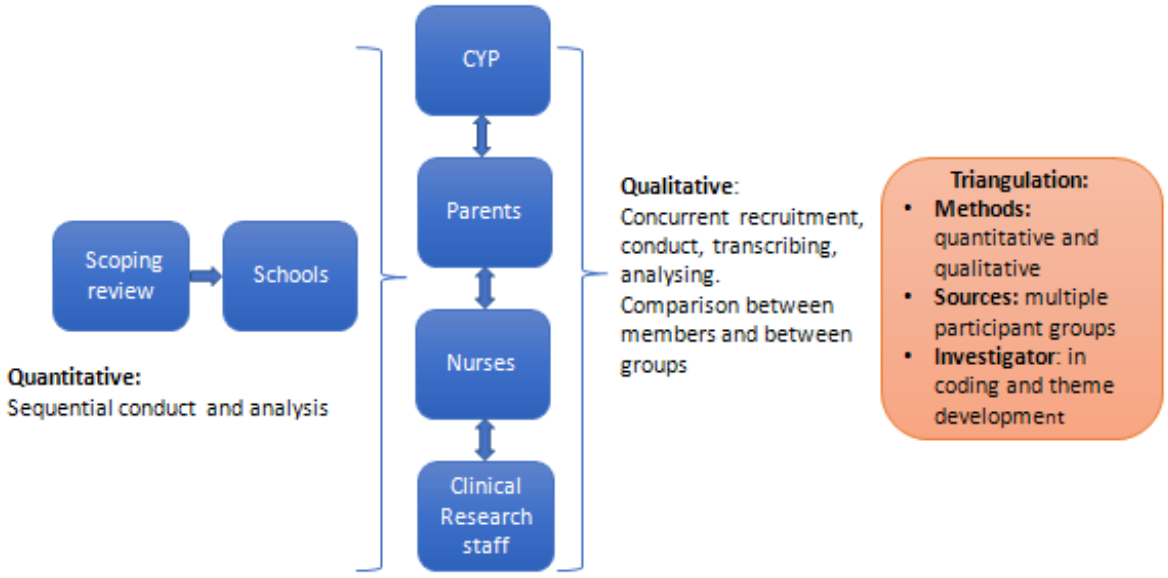
The term dependability is used instead of reliability in qualitative research (Lincoln and Guba, 1985). Dependability is demonstrated through a clear audit trail to enable the reader to review the decision-making process, the context of the research and demonstrate how the researcher reached their conclusions. The summary diagram Figure 6 and additional information within *Appendix 4* provide detail of the data analysis process. Lincoln and Guba (1985) also demand confirmability, with the audit or decision trail tracing the data directly

to the sources. Utilising the framework approach enabled each code to be cross-referenced to each individual. This also allowed discrepancies amongst an individual's responses to be reviewed, for example a participant who was coded as being very anxious about pain, stating they would definitely agree to participate in a PK study might seem at odds, but then this is modified by a statement that helping others is extremely important to them and to overcome their concern about pain they would request local anaesthetic cream. Having a transparent sequential process to coding enabled us to review alternative cases or discrepant voices and ensure interpretations were the most valid and plausible (Holloway and Wheeler, 2002).

Validity is linked to how 'true' or credible the findings of the study are and whether they accurately reflect the aims of the research and the social reality of participants (Hollaway and Wheeler, 2010). This concept of trustworthiness denotes how confident the reader can be in the findings (Lincoln and Guba, 1985). Remaining true to participants' experiences though 'thick description' is a fundamental principle within qualitative content analysis (Sandelowski, 2000b, Snelgrove and James, 2011). The results are therefore rich in participant accounts with coding grounded in participants' responses. Member checking of interpretation by participants is recognised as a strategy to enhance the validity of a study (Lathlean, 2010). This was not possible with the resources available of a lone researcher. Instead member checking took place within the interviews and focus groups by summarising, repeating or paraphrasing the participants words (Holloway and Wheeler, 2002). Participants will receive a copy of the results and be invited to provide comments. These will be taken into account in the write up for publication.

Triangulation, the process by which the phenomenon or topic is examined from different perspectives, has been achieved through methods triangulation (Holloway and Wheeler, 2002, Parahoo, 2014), with the five qualitative work streams all simultaneously recruiting, conducting, transcribing and analysing. In addition, researcher triangulation took place with initial coding and analysis by the researcher (JCM), with a second investigator (HPD) coding independently, reviewing codes and themes (see *Figure* 7 below) Researcher triangulation allows for cross checking to ensure that key themes are not missed (Giles, 2002, Rennie et al., 2002).

Figure 7: sequential analysis, with triangulation from methods, sources and coding methods



2.12 Conclusion

Chapter 2 has provided a summary of all the research design considerations made throughout the multiple work-streams of this project. There are a number of strategies researchers can use to ensure the dependability and trustworthiness of a qualitative research project. The predominant strategies utilised were a strong reflexive stance, member checking within the interview process, thick description of data, a clear audit trail with strong links to the data and methodological and data triangulation.

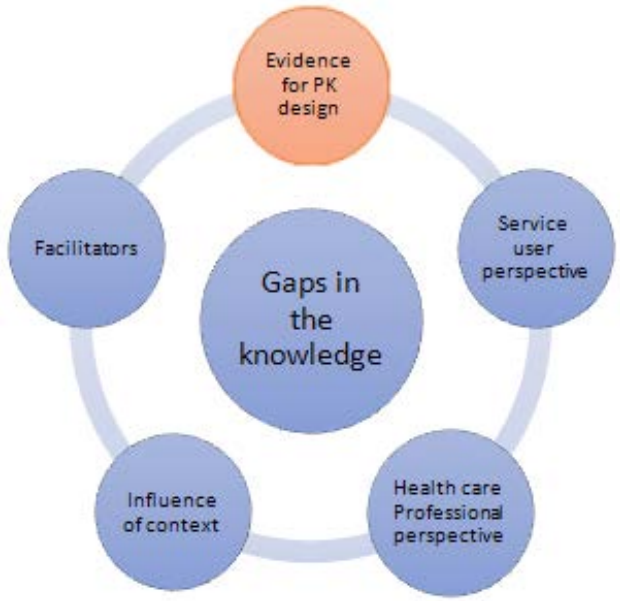
Chapter 3: A scoping review of recruitment of paediatric participants to pharmacokinetic research studies

3.1 Introduction

Pharmacokinetic studies are essential in paediatric patients as they help determine the correct dose and medication regimen (Thomson, 2000). However, less than a third of pharmaceutical trials conducted with adult participants funded by the UK's Medical Research Council (MRC) and Health Technology Assessment (HTA) programme recruited their original target within the time originally specified (Campbell et al., 2007). This is of concern because failure to recruit to target compromises the ability of the research to draw conclusions about a medication dose and regime (Campbell et al., 1997). In the context of Randomised Controlled Trials (RCTs), difficulty with patient accrual is the most commonly cited reason for discontinuation (Kasenda et al., 2014, Pica and Bourgeois, 2016). But even in this field little literature exists to guide researchers seeking to optimise recruitment (Patterson et al., 2015) or to reduce attrition from a study (Shilling et al., 2011, Tishler and Reiss, 2011). Pharmacokinetic studies have traditionally involved a rigid, experimental design with multiple blood samples from venepuncture (Patel et al., 2010, Choonara and Sammons, 2014). There is evidence CYP and parents find procedures involving needles particularly upsetting (French et al., 1994) so there are likely challenges to recruitment associated with this type of research. A systematic review of these challenges has not previously been conducted. In addition, alternative ways of conducting PK studies which minimise the number of blood samples or the total volume of blood required using micro-analytical techniques and population PK methods have been developed (Altamimi et al., 2016). The impact of these on recruitment and study retention has not been reviewed.

It is vital that future pharmacokinetic research is informed by systematic evaluation of past research. This will ensure that future research can build upon success in trial strategies and design in paediatric PK research, to minimise or address barriers to study recruitment and conduct. There is currently a gap in the knowledge surrounding the evidence for pharmacokinetic research design (see *Figure 8*). The first priority of PRESCRIBE was therefore to understand the current situation in pharmacokinetic research recruitment and trial conduct through a scoping review of the topic and integration of the research evidence.

Figure 8: gap in the knowledge: evidence for PK research design



3.2 Aims and objectives

The aim of this literature review was to explore what was known about the challenges and facilitators to recruitment and conduct of paediatric pharmacokinetic research within the published literature.

Objectives: Through a systematically conducted literature review, identify and quantify:

a. Strategies that improve recruitment to paediatric pharmacokinetic research studies
b. Barriers to recruitment[1] and conduct of paediatric pharmacokinetic research studies

[1]Barriers to recruitment are taken to include reasons why trials fail to recruit, including why potential participants decline participation within a study (Houghton et al., 2017)

3.3 Method

3.3.1 Search methods

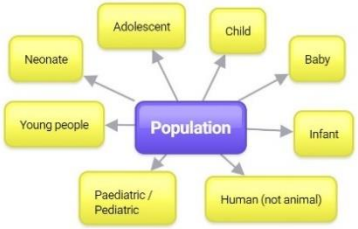
3.3.1.1 Scoping review

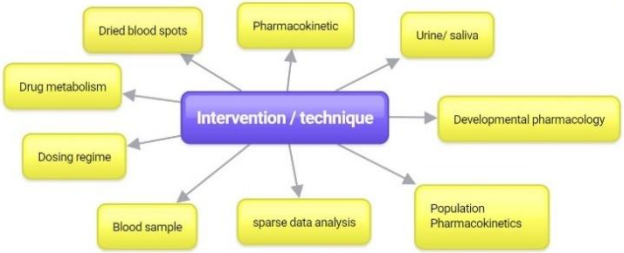
A Systematic literature review allows for objective appraisal of the evidence by identifying relevant studies, appraising their quality and summarising their results using a scientific methodology (Khan et al., 2003). Whilst systematic reviews are regarded as being one of the highest form of evidence that can be generated, this proved challenging to conduct where many of the trials being reviewed were classed as low levels of evidence. To achieve the objectives a scoping review was therefore adopted. Scoping reviews map the key concepts underpinning a research area and the main sources and types of evidence available. This approach can be used to examine the extent, range and nature of research activity and to identify gaps in the existing literature (Arksey and O'Malley, 2005). They can be useful where an area is complex or has not been reviewed comprehensively before (Mays et al., 2001). They are also useful at the first stages of a research project to inform the subsequent work by providing the researcher with relevant and quantified results about the knowledge on a particular topic (Hidalgo et al., 2011, Duffett et al., 2013).

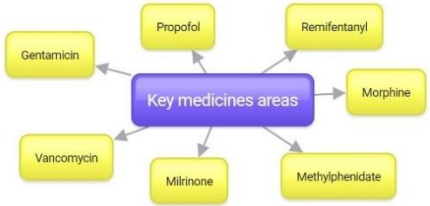
3.3.1.2 Refining search terms

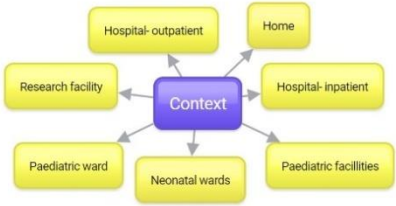
Mind mapping was used to generate possible search terms by consideration of the PICO format (population, intervention, control, and outcomes) a widely-used strategy for framing a research question (Sackett et al., 1997). The mind map informed several scoping searches conducted to identify if the terms were generating relevant articles (see *Figure 9* below).

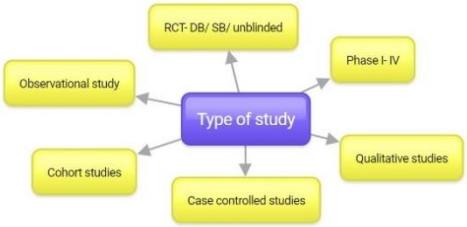
Figure 9: mind map of preliminary scoping review searches

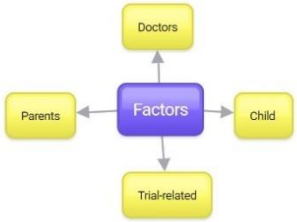


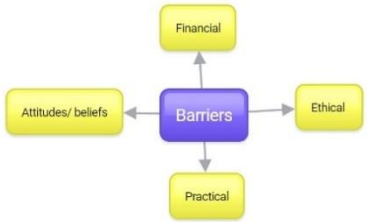












Where possible MeSH headings (Medical Subject Headings) were utilised (National Library Medicine, 2015) which is a controlled vocabulary thesaurus to promote accuracy of literature searching. From 1966 – 1988 'Kinetics' was suggested for pharmacokinetics and 'pharmacology' for pharmacodynamics. These produced an unmanageable quantity of irrelevant references, therefore the search was restricted to Pharmacokinetics. Defining the search terms for population was initially difficult. Using limits to restrict searches was not always successful at screening out adult and animal papers. The databases also had variations in the age categories the search could be limited to therefore limits were not used. Infant and child were universally accepted terms across the databases and proved relatively successful at screening out papers in adults and healthy volunteers and Pediatric was a MeSH heading which captured a vast range of terminology associated. The most difficult terms to refine were those capturing recruitment and study retention. The suggested MeSH heading was 'patient selection' however this failed to capture the phenomenon of trial recruitment alone. Although terms such as blood samples, drug study and research yielded a large number of papers when in conjunction with pharmacokinetics, many were not relevant and failed to discuss the phenomenon of recruitment.

Once the mind map was completed, scoping searches were conducted to determine whether the terms were generating relevant articles and were sufficiently comprehensive. A number of techniques were explored within the preliminary searches, before Pharmacokinetics was decided to be the most applicable. Recruitment and enrolment were selected to capture the phenomenon of recruitment. After this refinement process, the final search terms used for the review are defined in *Table 11* below.

Table 11: final search terms utilised for the scoping review

Search term:
1. pharmacokinetic* ti,ab
2. pharmacokinetic*.af
3. Recruit*. Ti, ab
4. Recruit*. Af
5. Enrol*. Ti, ab
6. Enrol*. Af
7. paediatric* OR pediatric* OR infant* OR child*. Ti, ab
8. paediatric* OR pediatric* OR infant* OR child*. Af
9. 3 OR 5
10. 4 OR 6
11. 1 AND 7 AND 9
12. 1 AND 7 AND 10
13. 2 AND 8 AND 10

3.3.1.3 Inclusion and exclusion criteria

To avoid bias in the selection process, inclusion and exclusion criteria were defined a priori. See *Table 12* below for full details of the inclusion and exclusion criteria.

Table 12: Inclusion & exclusion criteria for the scoping review

Component	Inclusion criteria	Exclusion criteria
Population	1. Children and young people (0-18 years old) who had participated in pharmacokinetic research. 2. No limitation on the number of participants per study. 3. No limitation on underlying disease process, type of medication, method or route of delivery. 4. No limitation on the type of samples analysed	1. Adult studies (over 18 yrs) 2. Studies in adult and paediatric patients where recruitment figures could not be separated for the two groups. 3. Animal studies 4. Studies in healthy volunteers
Intervention	1. Pharmacokinetic (PK) research 2. Population PK research	1. Pharmacodynamics studies 2. Pharmacogenomics 3. Genetics research 4. 'Routinely collected' therapeutic drug monitoring with no additional sampling for research purposes. 5. PK studies which measure non-therapeutic interventions, for example; environmental exposure to pollutants / toxic substances 6. PK studies which measure medication levels following indirect administration e.g., through the placenta or breast milk.

Outcome: **a. Facilitating strategies** **b. Barriers**	1. Proportion of eligible individuals recruited reported, e.g. 10/ 12 participants. 2. Proportion of eligible participants whose data was not included in the analysis reported 3. Identification of a facilitator that influenced potential trial participation to participate or stay participating in the study 4. Identification of a barrier that influenced potential trial participant to decline participation or be unable / unwilling to continue to the end of the study.	1. No failure to recruit e.g. 12/12 participants approached and consented **or** '12 people's data reported', with no indication of total sampling frame. 2. No loss of participants reported at the end of the study period e.g., 12/12 participant's data included 3. No report of facilitators which were attributed to success of recruitment 4. No report of barriers to recruitment or factors that led to the loss of participant data 5. No report of withdrawal and /or loss to follow up
Study design	1. Prospective experimental studies with / without randomisation. 2. Observational studies. 3. Studies conducted within phase(s) I- IV, including commercially funded and conducted studies 4. Qualitative studies of participation in pharmacokinetic research study 5. Papers reported in abstract only 6. Abstracts reported in English language 7. All reporting contained within the paper	1. Review papers 2. Studies which utilised therapeutic drug monitoring samples with no *additional* research specific sampling. 3. No abstract available in English language. 4. No direct contact to authors- detail had to be available within the published papers

3.3.1.4 Study design

A scoping review adopts an inclusive approach to studies (Arksey and O'Malley, 2005, Hidalgo et al., 2011). All studies that met the inclusion criteria were therefore considered for the review, regardless of study design.

3.3.1.5 Language

The plan was to screen non-English papers on their abstract. If the paper was not eligible on this basis then the reason was recorded as per other criteria. If the paper appeared to be eligible then attempts would be made to have these translated utilising local resources. If it was not possible to translate then their existence would be documented and 'language' recorded as the reason for exclusion (Centre for Reviews and Dissemination, 2009).

3.3.1.6 Year of publication

Searches were restricted to publications from 1990. A recent systematic review of invasiveness of PK studies (1967-2015) (Altamimi et al., 2016), found the majority of PK studies occurred from 1985 onwards (497/ 549 studies; 91%) which supported this strategy.

3.3.1.7 Electronic searches

Following preliminary searches, the electronic databases searched were:

- MEDLINE (1990- 8th August 2015)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) (1990- 8th August 2015)
- EMBASE (1990- 8th August 2015)
- ISI Web of Science (including Science Citation Index) (1990 –8th August 2015)
- Database of Abstracts of Reviews of Effects(DARE) (Centre for Reviews and Dissemination) (until April 2016 when funding ceased) (accessed 8th August 2015)
- Health Technology Assessment (HTA) database (online) (last updated October 2016) (accessed 8th August 2015)
- Cochrane Database of Systematic Reviews (accessed 8th August 2015)

The search strategy was reviewed and validated by two librarians who assisted with the decisions about using MeSH terms, the Boolean operators and the databases to access; a role recognised as an integral part of the review process (DeLuca et al., 2008). Eventually references to the same studies began to appear repeatedly and it was deemed reasonable to conclude that saturation had been reached. Duplicate citations were screened and removed as a function within EndNote software, a computer programme for reference management, with a system for storage and reference (Hidalgo et al., 2011), although deduplication by hand was also necessary.

3.3.1.8 Other searches

Although scoping reviews support the inclusion of literature identified through other strategies, such as citation searching, searching the reference lists of included retrieved and relevant studies and hand-searching key journals, the decision was made that this was not feasible. This was because included studies covered a variety of medications, locations, were conducted in a range of countries and published in 98 different journals. This heterogeneity reduced the feasibility of this method.

3.3.2. Data collection and analysis

3.3.2.1 Selection of studies

During the early scoping searches terms were searched in 'title and abstract' as well as 'all fields' for each of the key elements in Medline, Cinahl and Embase, to determine if searching in title and abstract alone was sensitive. The numbers for most searches were very similar therefore the decision was made to search title and abstract. Citations were imported into EndNote and tracked into categories for inclusion or exclusion. Potentially eligible papers were screened by the author (JCM), with independent screening of a sub-set of these (10%) by a second reviewer JFM (Supervisor). Full copies of potentially eligible studies were then obtained, reviewed by JCM, decision made on inclusion or exclusion of

papers based on the predefined criteria, with independent review by JFM. In the case of any differences of opinion a third reviewer KPM (second supervisor) reviewed and made the decision. There was no blinding to the journal, the authors or the institution.

3.3.2.2 Data extraction

A data extraction form was adapted from Polit & Beck (2010) (See *Appendix 6*). Data was extracted on the country in which the lead author was based, the setting, the nature of the medication under investigation, the nature of the included population, the number of participants recruited, the study design, the route and regime for medication administration, the sampling protocol and reasons for recruitment failure or data loss.

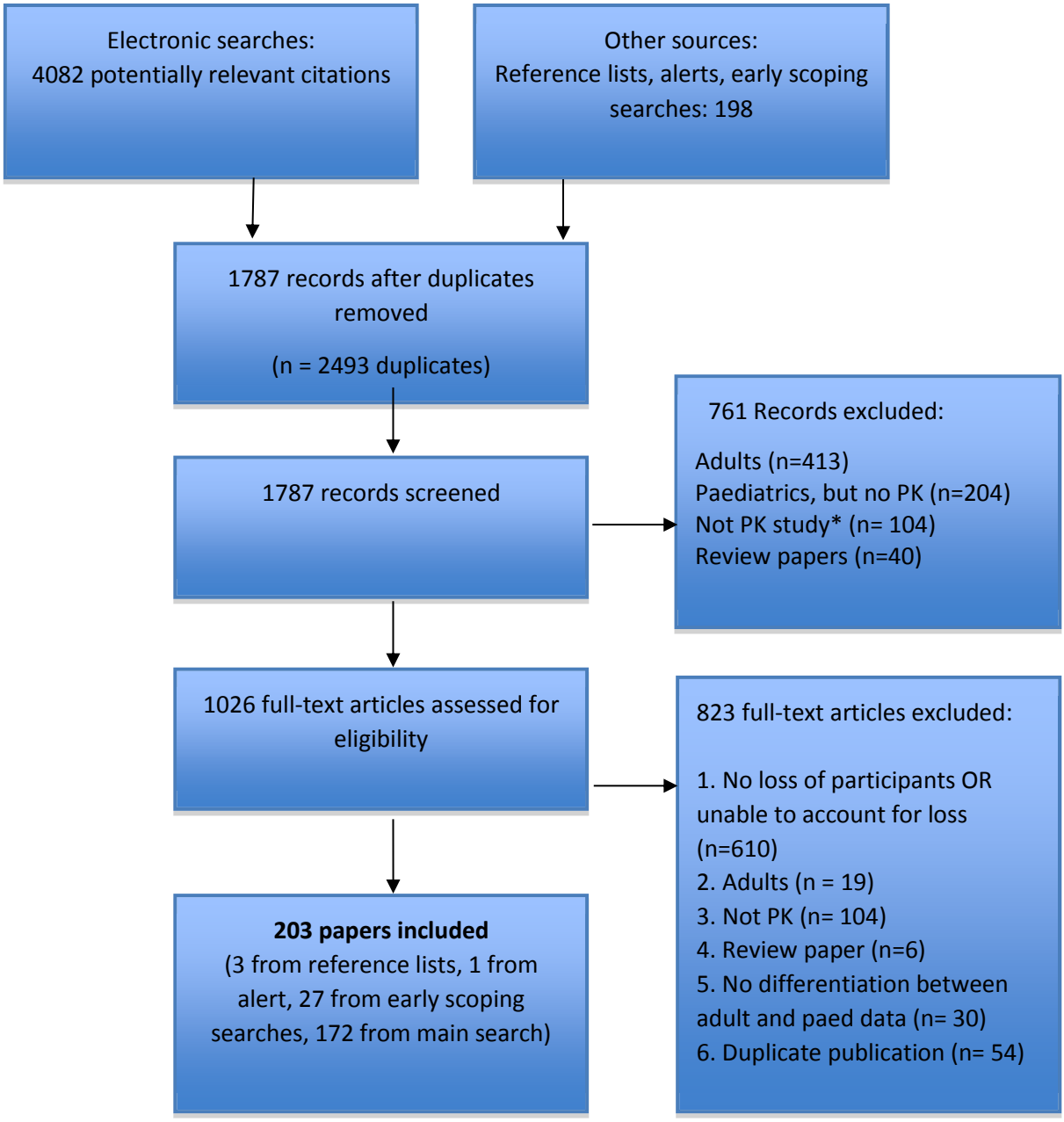
3.3.2.3. Analysis

The factor(s) that made the study eligible were extracted and then grouped together where they were similar in form and content. Broad categories were then shaped from the emerging themes and further delineation into sub categories by (JCM) with theme verification by (JFM). A study was eligible if it met one or more categories for inclusion therefore trials could appear in more than one category.

3.4 Results: included studies

The search strategy resulted in 4082 records being identified through database searches and a further 198 by other search methods, including the preliminary searches (*Figure 10* PRISMA diagram below). Following the removal of duplicates (2493), 761 records were excluded based on review of title and abstract and 1026 articles were reviewed in full. 823 were excluded, 610 of these because there was no reported participant loss or account for loss of participant data. 203 studies were eligible for inclusion (see *Table 13* below).

Figure 10: PRISMA diagram of reviewed studies 1990-2015



Codes for *Table 13* below.

[1]**Study design**: 1: RCT, 2: Open label study

[2]**PK approach**: C: 'classic' PK approach, P: Population PK, C&P: both

[3]**Category of medication**: A: Analgesia/ sedation, B: Chemotherapy, C: Anti-infective, D: HIV, E: psychiatric disorders, F: anti-convulsant, G: Acid suppression, H: asthma, I: other

[4]**Category of barrier:**

A: Recruitment, B: Medication- B1. Drug dose error, B2 Vomiting / expulsion, B3 Delivery issue, C: Sampling, D: Processing- D1. Clerical errors (includes labelling & discrepancies in drug history and collection times), D2: Technical failure, assay difficulties and preparation failure, D3 Storage and transportation. E: Withdrawal.

Table 13: table of all included studies within the scoping review

Authors	Yr published	Country	Study design[1]	PK approach[2]	No. centres	Category of medication[3]	Study population	No. eligible for PK	No. included in PK analysis	Age of CYP	No. samples & timeframe	Category
Kinney et al	1991	USA	1	C	1	I	Sepsis in NIC	170	35	<72hrs age	4 per infusion (0-7days). Max 12 samples/ pt	B1
Saxen et al	1993	Finland	2	C	1	C	NICU Patients	16	10	Neonates < 24hrs age	7 (0-72hrs) D1, D5 & D7 (total 21)	C
Fritz et al	1994	USA	2	C	1	I	Nocturnal enuresis	18	16	7-15yrs	4 (Wk 5, 7, 9, 11)	E
Husson et al	1994	USA	2	C	2	C	HIV	25	19	0.25-18yrs	9 (0-24hrs) D2 & D6. 10 (0-24hrs) D10 (total 28)	C
Blumer et al	1995	USA	2	C	MC: not listed	C	Infection	73	63	0.16 - 12yrs	7 (0-8hrs)	C, D2
Force et al	1995	USA	2	C	1	C	Otorrhoea after tympanostomy tube placement	10	7	3-8yrs	2 (pre-and 1 hr post dose) D7	C
Gaedicke et al	1996	Germany	2	C	3	B	Malignant tumours	49	24	3-15yrs	10 (0-24hrs)	E
Malinovsky et al	1996	France	2	C	1	A	Urology surgery	32	30	2-9yrs	13 (0-6hrs)	C
Reed et al	1996	USA	2	C	1	A	Sedation on PIC	29	19	0-18yrs	18 (0-24hrs)	C, D2
Birmingham et al	1997	USA	1	C	1	A	Orthopaedic surgery	28	28	2-12yrs	16 (0-16hrs)	C
Carlsson et al	1997	Sweden	1	C	1	I	Haemophilia A	21	14	>8yrs-42yrs	8 (0-48hrs)	A
Geiduschek et al	1997	USA	2	C	1	A	NICU patients on Extra-Corporeal Membrane Oxygenation (ECMO)	16	11	Neonates	4 (0-3 hours)	C
Gorodischer et al	1997	Canada	2	C	1	F	Epilepsy	170	128	0.3-18yrs	1 sample, no standardised time schedule (blood and saliva)	C, D2

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Mendelsohn et al	1997	USA	2	C	2	I	Congestive cardiac failure	9	6	2-18yrs	5 (0-2.5 hrs)	C
Stevens et al	1997	USA	2	C	2	C	Febrile neutropenia	28	23	0.5-16yrs	12 (0-120hrs) & 12 samples on D5 (total 24)	C
Reynolds et al	1997	USA	2	C	1	I	Elective surgery	29	28	0.25-5yrs	6 (0-4hrs)	C
Wintermeyer et al	1997	USA	2	C	1	D	HIV	16	13	0.25-18yrs	4 (1 per outpt visit)	C
Canafax et al	1998	USA	2	C	1	C	Otitis media	34	30	0.25-5yrs	2 (0.5-4hrs)	E
Lindsay et al	1998	USA	1	C	2	I	Septic shock	12	11	0.5-18years	6 (0.5-8hrs)	C
Peytchev et al	1998	Bulgaria	2	C	1	F	Epilepsy	59	48	1.7-12yrs	"steady state" no further info	E
Agertoft et al	1999	Denmark	2	C	1	H	Chronic asthma	13	10	3-6yrs	IV: 8 (0-3hrs), oral: 8 (0-6hrs) (total 16)	A, B3, E
Findling et al	1999	USA	2	C	1	E	Depression	30	23	5-17yrs	11 (0-24) & urine 4 (0-24hrs)	E
Crawley et al	2000	UK	1	C	1	F	Cerebral malaria	440	23	0.75-13yrs	8 (0-48hrs).	A, C, D2, E
Dallas et al	2000	Canada	2	C	1	D	HIV patients	6	3	0.33-5 yrs	8 (0-8hrs)	E
Hahn et al	2000	Denmark	2	C	1	A	Post-surgery	23	17	0.17 - 11yrs	5 (0-5 hrs) saliva and blood	C, D2
Kearns et al	2000	USA	2	C	3	C	Gram positive infection	57	54	0.25-16ys	<12mths: 8samples >12 months: 10samples (0-24hrs). (Total 10) Urine 4 samples (0-24hrs)	C
Nahara et al	2000	USA	2	C	1	A	Sedation in PIC	23	22	0.02 - 16yrs	"steady state" no further info	C
Scheepers et al	2000	Canada	2	C	1	C	Dental surgery	11	10	2-6yrs	12 (0-2hrs)	C
Stevens et al	2000	USA	1	C	27	D	HIV	106	77	0.25-18yrs	8 (0-4hrs)	C, D1

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Wulf et al	2000	Germany	2	C	1	A	Inguinal hernia repair	25	20	0-5yrs	9 (0-2hrs)	C
Johnson et al	2001	USA	2	C	7	I	Radiocontrast agent	43	40	0-12yrs	5 (0-32hrs)	C
Tod et al	2001	France	2	C&P	MC: not listed	C	Herpes simplex & Varicella Zoster Virus	85	79	<2yrs	5 (0-8hrs)	D1
Reed et al	2001	USA	1	C	8	A	Sedative pre-med for day surgery	111	89	0.5-16yrs	13 (0-10hrs)	B2, C
Ross et al	2001	USA	2	C	2	A	Surgical patients	42	34	0-18years	< 2yrs: 10 samples 0-1hr >2 yrs 12 samples (0-4hrs) (total 12)	C, D2
Dsida et al	2002	USA	2	C	1	A	Orthopaedic / urology pts	43	36	1-16yrs	16 (0-10hrs)	C
Furman et al	2002	USA	2	C	MC: not listed	B	Refractory leukaemia	49	33	<21yrs	4 (0-24hrs)	C
Guay et al	2002	USA	2	C	1	I	Prevention HIV vertical transmission	29	21	Newborn	4 (1hr- 14weeks age)	C
Gremse et al	2002	USA	1	C	11	G	Gastro oesophageal reflux	60	53	1-11yrs	13 (0-24hrs)	B1, C, D3
Lipman et al	2002	Australia	2	C	1	C	Sepsis	20	17	0.25-5yrs	9 (0-12hrs) D0, D2, D6-8 (Total 27)	C, D1
Marina et al	2002	USA	2	C	MC: not listed	B	Solid tumours	22	10	<21yrs	7 (0-48hrs)	D1
Orenstein et al	2002	USA	1	C	6	G	Gastro oesophageal reflux	29	25	4-11yrs	10 (0-6hrs)	C
Rahman et al	2002	USA	1	C	1	I	Malnourished children	411	339	1-2.1 yrs	3 (D0, D21, 3 months)	E
Rongkavilit et al	2002	Netherlands	2	C	1	D	Neonates exposed to HIV	24	22	<0.08yrs	6 (0-12hrs) D14 & D28 (total 12)	D2, E
Best at al	2003	USA	2	C	5	I	Children with Kawasaki disease	24	10	0.5-5 years	D1:6 (0-5hrs), D6: 4 (0-3hours) (total 10)	B1, C, E

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de Wildt et al	2003	Netherlands	2	C	1	A	Sedation in Paediatric Intensive Care (PIC) neonates	21	20	0.005-17yrs	3 samples (loading dose), 1 sample /day on infusion, 9 (0-24hrs) post infusion (total: min 13)	E
Fraaj et al	2003	Netherlands	2	C	1	D	HIV	35	6	0.2-13.6yrs	8 (0-8hrs) D1 & D2 (total 16)	C, E
Gajjar et al	2003	USA	2	C	MC: not listed	B	Glioma with concomitant enzyme inducing anti-convulsant	35	18	3-21yrs	7 (0-6hrs) D5 and D12 (total 14)	E
Howel & Patel	2003	UK	1	C	1	A	Elective spinal surgery	24	22	>25kgs	4 (2-5hrs)	B1
Kearns et al	2003	USA	2	C	1	A	Healthy children	12	12	5-15yrs	12 (0-9.6 hrs)	C
Sallas et al	2003	USA	1	C&P	47 centres in 8 countries	F	Epilepsy	138	109	3-17yrs	4 (visits 5,6,7,8)	C
Wu et al	2004	USA	2	C	1	I	Neonatal Intensive Care (NICU)	59	22	<1 month	2 (D14 & D 28)	A, E
Aquino et al	2004	Canada	2	C	MC: not listed	B	Refractory solid tumours	23	22	<21yrs	13 (0-6hrs)	D1
Conway et al	2004	UK	2	C	1	C	Cystic Fibrosis	5	4	<16yrs & >16yrs	8 (0-12hrs) D1 & D14. 2 (0-2hrs) D8 & D11 (total 20)	A, E
Fletcher et al	2004	USA	1	C	48	D	HIV	21	18	3-14yrs	7 (0-8hrs)	C
Goren et al	2004	USA	2	C	1	B	Tumours	14	11	1-18yrs	8 urine D1 and D5 (total 16)	C
Lebovitz et al	2004	USA	2	C	1	H	Asthma in PIC	56	50	0.5-16yrs	13 (0-72hrs)	B1, C
Neville et al	2004	USA	2	C	MC: not listed	B	CNS tumour	26	25	<22yrs	11 (0-48hrs) 16pts. 9 pts had additional 3 (8-12hrs)	C

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Oliver et al	2004	USA	2	C	1	I	Cardiopulmonary bypass for congenital heart surgery	30	28	<16yrs	8 (0-4hrs)	C
Quinn et al	2004	Canada	1	C	3	E	ADHD	32	31	9-12yrs	9 (0-10hrs)	E
Stewart et al	2004	USA	2	C	4, 2 Countries	B	Medulablastoma & supratentorial tumour	44	36	3-21yrs	6-8(0-6hrs)	B3
Wagner et al	2004	Germany	2	C	MC: not listed	B	Progressive glioma	9	7	3-18years	7 0-24hours	C, E
Wheeler et al	2004	USA	2	C	1	A	Elective surgery	10	10	5-11yrs	16 (0-10yrs)	C
Bergschoeff et al	2005	Netherlands	1	C	2	D	HIV	24	20	2-13yrs	8 (0-12hrs) wk 4 & Wk 8 (Total 16)	B1
Capparelli et al	2005	USA	2	C	MC: not listed	C	Bacterial infection	111	98	0.5-16yrs	12 (0-24hrs)	B2
Chalkiadis et al	2005	Australia	2	C&P	8	A	Surgical infants	22	12	<0.25 years	5 (0.5-4hrs)	C
Chien et al	2005	USA	2	C	5	C	Bacterial infection	85	80	0.5-16yrs	IV: 2 (0-24hrs) oral 1 (0-24) + 36 and 48hr samples (total 5)	B2, D1, E
Daw et al	2005	USA	2	C	MC: not listed	B	Malignant solid tumour	17	17	<22years	7 (0-24hours)	A
Jacobs et al	2005	USA	2	C	3	C	IV in Inpatient / outpatient	32	29	0.5-16yrs	<2 yrs:7, >2: 9. (0=168 hrs)	C, E
Kyllonen et al	2005	Finland	2	C	1	A	Minor surgery/ orthopaedic surgery	24	20	0.02 - 1year	10 (0.3-10hrs)	B2
Saul et al	2005	USA	1	C	48 centres, 7 countries	I	Cardiac arrhythmias	32	25	0.08 - 16yrs	Loading dose: 5 samples (0-2hrs), 3 (0-24hrs), washout 9 (0-30days) (total 17)	C
Veal et al	2005	UK	2	C	7	B	Chemotherapy	31	16	<21yrs	8 (0-24hrs)	C
Ward et al	2005	Canada	1	C	1	I	Osteogenesis Imperfecta Type 1	25	24	4-16yrs	Urine: 3 (0-24hrs)	B2

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Bomgaars et al	2006	USA	2	C	1	B	Refractory solid tumours	23	11	1-21yrs	15 (0-24hrs)	C
Cormack et al	2006	UK	2	C	1	A	Chronic Liver disease	17	16	3-15yrs	6 (0-8hrs)	C
Dupuis et al	2006	Canada	2	C	1	I	Stem cell transplant	80	24	0.5-16.9yrs	8 (0-12hrs)	A, B2, C, E
Fouladi et al	2006	USA	2	C	MC: not listed	B	Refractory solid tumours	18	12	<22yrs	11 (0-6hrs) Wk 1 & Wk3 (total 22)	c, D3
Heresi et al	2006	USA	2	C	MC: not listed	C	Premature neonates in NIC	23	19	premature infants	6 (0-12hrs)	C
Johannsen et al	2006	USA	2	C	13	B	Malignancy	31	26	<21yrs	15 (0-96hrs)	B2, C
Kokki et al	2006	Finland	2	C	1	A	Surgery	34	30	0.5 -7.6yrs	10 (0-12hrs)	A, B2, C
Muller et al	2006	Germany	2	C	1	A	Post-operative pain in PIC	41	39	0-4yrs	8 (012hrs) Urine 4 (0-12hrs)	C
Mehta et al	2006	USA	2	C	1	C	Stem cell transplantation	14	12	0.38 -9yrs	14 (0-168hrs) Wk 1& 4. (Total 28)	C
Rodriguez-Galindo et al	2006	USA	2	C	1	B	Refractory solid tumours	11	10	<21yrs	D1-5: 4 samples /day 0-6 hrs. (total 20)	E
Simpson et al	2006	Australia	2	C&P	5, 4 countries	I	Malaria	86	70	1.3-10yrs	3 (0-24hrs)	B2
van der Lee et al	2006	Netherlands	2	C	1	D	HIV	19	18	1.4-12.9yrs	8 (0-24hrs) D14	E
Zhao et al	2006	USA	1	C	1	G	Gastro oesophageal reflux	30	27	1-11yrs	9 (0-6hrs)	E
Zuppa et al	2006	USA	1	C	1	I	Neonatal cardiac surgery	16	15	Neonate	13 (0-24hrs)	C
Aman et al	2007	USA	2	C	1	E	Psychiatric / neurodevelopmental conditions	19	12	4-15yrs	4 (0-7 hours)	C
Broniscer et al	2007	USA	2	C	MC: not listed	B	Recurrent brain tumours	50	28	<21yrs	7 (0-6 hrs)	A, C
Diaz et al	2007	USA	2	C	1	A	Surgical patient on PIC	10	10	0.3-7.9yrs	12 (0-8hrs)	D1

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Fouladi et al	2007	USA	2	C	1	B	Refractory solid tumours	26	18	3-22 yrs	9 (0-24hrs)	A, D2
Horton et al	2007	USA	2	C	MC: not listed	B	Refractory leukaemia	11	5	1-21yrs	Unable to determine	A
Kulkarni et al	2007	India	1	C	1	A	Children undergoing minor surgery	50	29	3-12years	9 (0-12hrs)	A, C
Lynn et al	2007	USA	1	C&P	1	A	Elective surgery	25	15	0.5-1.5yrs	5-7 samples (0-12hrs)	B1, C
Quinn et al	2007	Canada	1	C	1	E	ADHD	18	14	6-12yrs	11 (0-24hrs)	B1
Veal et al	2007	UK	2	C	9	B	Neuroblastoma	29	28	<18yrs	5 (0-6hrs) D1 and D14 (total 10)	C
Zhang et al	2007	USA	2	C&P	8 in USA	D	HIV	52	43	5-17yrs	5 (0-12hrs) & 4 trough levels (wk2, 8, 16 24) (total 9)	D1
Abdel-Rahman et al	2008	USA	2	C	MC: not listed	C	Gram positive infection	25	22	2-17yrs	10 (0-24hrs)	B3, C
Almeida et al	2008	Portugal	2	C	1	F	Epilepsy	31	26	2-17yrs	7 (0-12)	E
Bomgaars et al	2008	USA	2	C	1	C	Children receiving chemotherapy	37	32	2-18yrs	8 (0-8hrs). Urine 0-8 hrs	C, D3
Danne et al	2008	Germany	1	C	1	I	Type 1 Diabetes	32	30	6-17yrs	14 (0-16hrs)	C
Findling et al	2008	USA	2	C	4	E	Psychiatric disorder	21	19	10-17yrs	9 (0-24hrs) D 14	E
Glade Bender et al	2008	USA	2	C	MC: not listed	B	Malignant solid tumour	10	8	<22years	D1: 4 (0-5hrs), D2-14: 5 samples (total 9)	C
Goto et al	2008	Japan	2	C	1	I	Liver transplant	44	39	0.25-14yrs	2 samples D3 and D7 (total 4)	E
Gururangan et al	2008	USA	2	C	MC: not listed	B	Recurrent brain tumours	41	23	<21yrs	8 (0-4hrs)	A, C, D2, E
Hammer et al	2008	USA	1&2	C	MC: not listed	I	Surgical patients	77	76	0.06-12yrs	<2ys 3 (0-post infusion), >2yrs: 4 samples (0-post infusion) (total 4)	B3
Neville et al	2008	USA	2	C	2	H	Asthma	25	24	<16yrs	14 (0-60Hrs)	C

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Standing et al	2008	UK	2	P	1	A	Day surgery	74	70	1-12yrs	3 samples: insertion of cannula, end of surgery & removal of cannula	A, B2
Van Ommen et al	2008	Netherlands	2	C	1	I	Veno-thromboembolic disease	84	76	0-18yrs	1 (4 hrs) and if dose altered (min 1)	C
Almenrader et al	2009	Italy	2	C	1	A	Induction of anaesthesia for umbilical procedures	13	10	1.8- 7 yrs	8 (0.33-12hrs)	C
Baruchel et al	2009	Canada	2	C	5	B	Recurrent CNS tumours	7	5	2-18yrs	10 (0-48hrs)	E
Beghetti et al	2009	Switzerland	2	C	11 in 7 countries	I	Pulmonary hypertension	36	35	2-12yrs	6 (0-12hrs)	B1
Chadwick et al	2009	USA	2	C	9 in 2 Countries	D	Infants with HIV	10	9	>14days - <6 weeks	5 (0-12hrs), 4 (8-24 Wks) (total 9)	B2
Gonzalez et al	2009	USA	1	C	1	E	ADHD	27	23	6-12yrs	9 (0-16hrs)	C
Hahn et al	2009	Germany	2	C&P	14 sites in Europe & Canada	I	MRI contrast agent	138	130	2-17yrs	4 (0-8hrs)	B1, C, D2
Jacquemin et al	2009	France	1	C	1	I	Chronic cholestasis or Cystic Fibrosis	12	11	0-18yrs	6 (0-24hrs)	C
Malloy et al	2009	USA	1	C	5	I	Type II diabetes	13	6	10-16yrs	3 (0-8hrs)	D2
McGregor et al	2009	USA	2	C	MC: not listed	B	Refractory solid tumours	13	6	1-22yrs	5 (0-14days)	A, D2
Nielsen et al	2009	Sweden	2	C&P	1	C	Neonates	61	61	0-45 days	2 (0.25-8hrs) D2 & D5 & routine measurements (min 4)	D1
Pollock et al	2009	UK	2	C	1	D	HIV	43	37	0-16yrs	5 (0-12hrs)	B1, C
Saez-Llorens et al	2009	USA	2	C	MC: not listed	C	Herpes simplex or Varicella Zoster Virus	51	50	1-12yrs	6 (0-5hrs)	B1

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Saez-Llorens et al	2009	USA	2	C	8 in 3 countries	C	Infants with candidiasis	18	17	<0.25yrs	1 dose: 3 samples (0-24hrs), multiple doses: D1 5 samples (0-24hrs), D4 (2: 1 & 24hrs) (total 10)	C
Beaty et al	2010	USA	2	C	8	B	Refractory solid tumours	124	49	<21yrs	4 (0-7days)	A, D2
Blumer et al	2010	USA	2	C&P	5	C	Herpes simplex	18	17	0.08-1yr	4 (0-6hrs)	B2
Fouladi et al	2010	USA	2	C	MC: not listed	B	Refractory CNS tumours	59	33	<21yrs	7 (-0-8hrs)	A, C
Gururangan et al	2010	USA	2	C	MC: not listed	B	Malignant glioma	31	12	<21years	3 (0-16days)	B1
Kimberlin et al	2010	USA	2	C	15	C	Herpes simplex	112	98	0.08-11yrs	6 (0-6hrs)	B2
Mckibbin et al	2010	USA	2	C	1	B	Medullablastoma	49	33	3-21yrs	8 (0-3hrs) after 1st & 2nd doses (total 16)	A, D2
Musiime et al	2010	Uganda	2	C	2	D	Children with HIV	41	36	3-12yrs	7 (0-12hrs) + D28 8 (0-24) Total = 15	D1
Standing et al	2010	USA	2	P	1	A	Cranioplasty	7	7	0.3-1yr	11 (0.08-4.5 hrs)	C
Su et al	2010	USA	2	C&P	1	A	Cardiac surgical patients on PIC	38	36	Infants	14 (0-24hrs)	C
Aplenc et al	2011	USA and Canada	2	C	21	B	Solid tumours	39	19	1-21yrs	10 (0-24hrs)	A
Berg et al	2011	USA	2	C	MC - not listed	B	Solid tumours	49	29	1-21yrs	9 (0-D14)	A
Chadwick et al	2011	USA	2	C	17	D	Infants with HIV	31	20	0-0.5yrs	5 (0-12hrs)	B1, C, E
Fillekes et al	2011	Uganda	2	C	2	D	HIV	41	39	3-12yrs	9 (0-4wks)	D1
Forbes et al	2011	USA	2	C	11	I	Intravascular procedures	110	106	0-16yrs	6 (0-30mins after stop infusion)	C
King et al	2011	USA	2	C	1	D	HIV patients	50	47	8-18yrs	7 (0-24hrs) & 3 Urine (0-24hrs)	C

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Kiser et al	2011	USA	2	C	MC- not listed	D	Children with HIV	195	172	0.24-21yrs	9 (0-24hrs)	B1, B2, C, D3
Knoderer et al	2011	USA	2	C	1	C	Post cardiac surgery on cardiopulmonary bypass	16	15	0.08-3yrs	7 (0-12days)	B1
Lynn et al	2011	USA	1	C&P	1	A	Post-surgery	25	14	0.17-0.5yrs	5-7 samples (0-12hrs)	C, E
McJunkin et al	2011	USA	1	C	MC- not listed	C	La Crosse Encephalitis	15	9	5-14yrs	6 (0-4 days)	D1
Mugabo et al	2011	South Africa	2	C	1	D	Premature infants born to HIV-infected women	68	58	Infants <37wks gestation	7 (0-21days)	C
Piper et al	2011	USA	2	C	1	C	Infants with suspected candidiasis	10	8	0.0005-0.16yrs	8 (0-5 days)	B1, D1
Raber et al	2011	USA	2	C	12 sites in 6 countries	I	Glaucoma	47	46	0-18yrs	5 (0-1hr)	D3
Rakh-Manina et al	2011	USA	2	C	1	D	HIV	50	44	4-18yrs	7 (0-12hrs)	B1, C
Warren et al	2011	USA	2	C	MC - not listed	B	Brain tumour	23	18	0-21yrs	6 (0-24hrs)	A, B1, B3, C
Wigal et al	2011	USA	2	C	1	E	ADHD	32	28	6-12yrs	8 (0-11.5hrs)	C
Ademisoye et al	2012	Nigeria	2	C	1	I	Sickle cell disease	15	10	10-13yrs	14 (0-28days)	E
Chamberlain et al	2012	USA	2	C&P	10	F	Status epilepticus	69	63	0.25-17yrs	13 (0-48hrs)	C, E
Cohen-Wolkowiez et al	2012	USA	2	C&P	5	C	Premature neonates in NIC	32	31	<32weeks	5 (0-24hrs) + 1 (pre-last dose)	D1
Drover et al	2012	USA	2	C	1	A	Post-operative Adolescents	20	18	12-17yrs	10 (0-24hrs)	B1 & C
Fillekes et al	2012	Netherlands	2	C	1	D	Infants with HIV	16	15	0.08-25yrs	4 (0-12hrs)	B1
Jimenez et al	2012	USA	2	C	1	A	Tonsillectomy	70	68	3-17yrs	6 (0-240mins)	B1

Authors	Yr published	Country	Study design[1]	PK approach[2]	No. centres	Category of medication[3]	Study population	No. eligible for PK	No. included in PK analysis	Age of CYP	No. samples & timeframe	Category
Malhotra et al	2012	USA	2	C	7	I	Overactive bladder	21	16	8-17yrs	4 (0-4hrs Wk 4) + 4 (8-20hrs Wk 8) = 8 total	B1, C
Manitpisitkul et al	2012	USA	1	C&P	17 in 5 countries	F	Epilepsy	50	35	0.1-2yrs	4 (0-10hrs)	B1, C
Mcgregor et al	2012	USA	2	C	1	B	Solid tumours	20	11	0-21yrs	7 (0-6hrs) on D1 and last day course 1 = 14 total	A
Norman et al	2012	Unknown	2	C	Not specified	I	Type 1 Diabetes	16	13	10-17yrs	12 (0-4hrs)	B3
Oudijk et al	2012	Zambia	2	C	1	D	Children with HIV	29	22	0.7-3.2 yrs	4 (0-6 hrs)	B1
Varendi et al	2012	Estonia	2	C	1	A	Clinically indicated paracetamol	39	30	0-2yrs	Up to 5 (no time frame specified)	A
Autmizguine et al	2013	Canada	2	C	1	C	Osteoarticular infections	12	11	0-18yrs	5 (0-6hrs)	C
Blaney et al	2013	USA	2	C	MC- not listed	B	Neoplastic meningitis	19	6	3-22yrs	2 (Wk 1& 3) CSF	A
Cohen-Wolkowiez et al	2013	USA	2	C&P	3	C	Premature neonates in NIC	24	23	<32weeks	5 (0-8hrs)	C
Demirjian et al	2013	USA	1	C	1	C	Infection	61	46	2-18yrs	4 (0-32hrs)	C
Glade Bender et al	2013	USA	2	C	MC - not listed	B	Solid tumours	51	43	2-22yrs	11 (0-24hrs)	A, C
Gore et al	2013	USA	2	C	MC- not listed	B	Refractory solid tumours	15	13	1-18yrs	27 (0-4 wks)	E
Hummel et al	2013	USA	2	C	MC- not listed	B	Brain tumour	19	16	12-21yrs	9 (0-24hrs)	A
Kilburn et al	2013	USA	2	C	MC- not listed	B	Brain tumour	24	9	3-21yrs	8 (0-10hrs) + 1 (D7) + 1 (D21) = 10 total	A, B3,
Kim et al	2013	USA	2	C	MC - not listed	B	Neurofibromatosis	9	4	3-18yrs	7 (0-8hrs)	C
Kimberlin et al	2013	USA	2	C	16	C	Influenza	87	77	0-2yrs	5 (0-12hrs)	A, C, E

Authors	Yr published	Country	Study design[1]	PK approach[2]	No. centres	Category of medication[3]	Study population	No. eligible for PK	No. included in PK analysis	Age of CYP	No. samples & timeframe	Category
MacDonald et al	2013	USA	2	C	MC- not listed	B	Glioma	30	24	<22yrs	4 (0-6hrs)	A
Min et al	2013	Korea	2	C	1	I	Post kidney transplant	38	34	5-15yrs	15 (0-24hrs) on D7, D14 & D28 (total = 45)	C
Muscal et al	2013	USA	2	C	MC -not listed	B	Solid tumours	23	6	12-22yrs	13 (0-72hrs)	A
Salzer et al	2013	USA	2	C	MC- not listed	B	Leukaemia	59	41	2-18yrs	12 (0-24hrs) D1	B1, D1
Shah et al	2013	UK	2	c	6	F	Epilepsy	102	100	0-17yrs	3 (0-8 wks)	C
Smith et al	2013	USA	2	C	MC- not listed	I	Urea cycle disorders	15	13	0.08-6yrs	4 (0-24hrson D1) + 4 (0-24hrs on D10) = total 8. Urine 3 (0-24hrs D1) + 3 (0-24 on D10) = 6	C
Stricker et al	2013	USA	2	p	1	I	Craniofacial surgery	39	18	0.5-2yrs	10 (0-15hrs after end of infusion)	A
Sugita et al	2013	Japan	2	C	1	C	Otitis media	23	20	0.4-5.25yrs	2 (0-4.8hrs) Blood & ear effusion	C
Thompson et al	2013	USA	2	C	MC - not listed	B	Refractory solid tumours	20	18	>1-<22yrs	8 (0-48hrs)	E
Veal et al	2013	USA	2	P	MC - not listed	B	Neuroblastoma	103	73	0-21yrs	6 (0-14days)	C
Vrooman et al	2013	USA	2	C	10	B	Leukaemia / Lymphoma	30	23	1-17yrs	4 (0-72hrs)	B1, C
Walson et al	2013	USA	1	C	1	A	Temperature prophylaxis	30	26	0.25-0.5yrs	3 (0-8hrs)	B1, C
Weinstock et al	2013	USA	2	C	24	F	Epilepsy	50	49	0.08-16yrs	3 (0-8hrs)	B3, C
Zorzi et al	2013	Canada	2	C	MC- not listed	B	Solid tumours	12	5	>1-<18yrs	8 (0-24hrs) + 1 (D15) = 9 total	A
Altcheh et al	2014	Argentina	2	P	1	C	Chagas Disease	40	37	2-12yrs	3 (0-6hrs)	A, E
Boddy et al	2014	UK	2	C&P	MC- not listed	B	Cancer	101	96	Not specified	8 (no range)	E
Bradley et al	2014	USA	2	C	8	C	Bacterial infection	24	19	0.25-2yrs	6 (0-12hrs)	C

Authors	Yr published	Country	Study design[1]	PK approach[2]	No. centres	Category of medication[3]	Study population	No. eligible for PK	No. included in PK analysis	Age of CYP	No. samples & timeframe	Category
Bunupuradah et al	2014	Thailand	2	C	2	D	HIV	20	18	6-18yrs	8 (0-24hrs)	B1
De Bruyne et al	2014	Belgium	2	C	1	I	Nocturnal enuresis	23	22	5-8yrs	3 (1-6hrs)	B3
Desai et al	2014	USA	2	C	1	B	Neuroblastoma	14	14	0-15yrs	15 (0-28days)	C
Garcia et al	2014	Argentina	2	P	5	C	Chagas Disease	81	76	0-12yrs	5 (no times provided)	B1
Hiruy et al	2014	USA	2	C	1	I	TB	36	31	<10yrs	6 (0-24hrs)	A
Kukulka et al	2014	USA	2	C	3	G	Gastro oesophageal reflux	36	31	1-11yrs	14 (0-24hrs)	C, E
Musiime et al	2014	Uganda	1	C	2	D	HIV	79	59	0.25-13yrs	7 (0-12hrs Wk1), 7 (0-12hrs, Wk8) (total =14)	B1, B2, C, E
Oualha et al	2014	France	2	C	1	I	Post cardiac surgery low cardiac output	55	39	0-18yrs	3 (0-6 hrs post infusion commencing)	C
Ramos-Martin et al	2014	UK	2	P	1	C	Infection	39	39	0-16yrs	4 (1-24hrs) & 4 after last dose (1-24hrs) (total 8)	C, D1
Thompson et al	2014	USA	2	C	MC- not listed	B	Cancer	107	98	0-21yrs	20 (0-72hrs)	E
Zongo et al	2014	Burkina Faso	2	C	3	I	Malaria	379	365	>0.5-10yrs	2 (D7)	B1, B2, E
Woloszczuk-Gebicka et al	2014	Poland	2	C	1	A	Abdominal surgery	20	20	0.3-3yrs	3 (0-48 hrs) + 3 (3-18hrs post infusion) = 6	C
Hahn et al	2015	USA	2	P	1	C	Infection	15	13	0-18yrs	2 additional (1 hr post, & 3/ 4 hrs post)	C
Kilburn et al	2015	USA	2	C	MC- not listed	B	CNS tumour	33	16	0-22yrs	8 (0-72hrs) + 6 (0-24hrs on D28) = 14 total	A
Kim et al	2015	USA	2	C	MC - not listed	B	Solid tumours	20	10	2-21yrs	2 (0-12hrs)	A

Authors	Yr published	Country	Study design[1]	PK approach[2]	No. centres	Category of medication[3]	Study population	No. eligible for PK	No. included in PK analysis	Age of CYP	No. samples & timeframe	Category
Munoz et al	2015	USA	2	C	40 in 3 countries	C	Influenza	17	16	0-12yrs	8 (D1- 0-12hrs), 4 (D3- pre-8 hrs) (12 total)	C
Stricker et al	2015	USA	2	P	1	I	Posterior Spinal Fusion Surgery	21	20	12-17yrs	max 11 (0-6 hrs post infusion)	A
Young et al	2015	USA	2	C	23 in 8 countries	I	Haemophilia A	71	51	0-12yrs	Unclear (0-48hrs)	A, C, E

3.4.1 Details of the included studies

Journal: The included studies were reported in 99 journals, making hand searching unfeasible. The highest numbers were from the Journal of Clinical Oncology (n=12), Antimicrobial Agents and Chemotherapy (n=10), Clinical Cancer Research (n=10), Pediatric Blood and Cancer (n=10) and Pediatric Infectious Disease Journal (N=10).

Country of origin: Just under two-thirds of the papers originated from USA 65% (n= 132), 5% from the UK (n=11) and 5% (n= 11) from Canada. The remaining 25% originated from 24 other countries. In one paper, the country where the study was conducted could not be determined.

Number of sites: The included studies were single site studies in 48% of cases (n=98). A number were reported to be multi-centre but the exact number of sites was indeterminable (n=43, 21%). The highest number of sites was a multi-centre study with 48 centres in 8 countries.

Trial design: 170 were classified as observational studies (84%) and 31 (16%) occurred in the context of an RCT. Most described a 'classic' approach to PK with a predetermined sampling regime (n=178, 88%), 9 studies utilised a population PK modelling approach only (4%) and 16 studies (8%) used a combination of the two approaches.

Subject area: Medications within the included studies were classified according to 8 main classifications. Analgesia / sedative medications (n=49, 24%), anti-infective medications (n=38, 19%) and chemotherapy (n=32, 16%) were the biggest categories.

Year of publication: The number of publications (which met the inclusion criteria) had increased significantly over the past seventeen years. 89% (n=181) of papers came from

2000 onwards and 69% (n=141) of papers came from 2005 onwards, possibly reflecting changes in legislation internationally. The reduction in numbers for 2015 reflects the searches running until 5th August 2015.

Number of participants: The number of patients included within the PK study varied widely from 3 to 365 (median of 23). 15% of the studies (n=30) had 10 or less participants in the study, 45% (n=91) had 20 or less participants and 84% of the studies (n=165) had below 50 patients in them. Only 9 studies (4%) had 100 or more participants.

Age of participants: Studies were categorised into those involving infants (under 1 year of age) (n=108, 53%), children (1- 12 years) (n=181, 89%) and adolescent studies (age 13years plus) (n=123, 61%). Many studies had broad inclusion criteria and crossed several age classifications and were counted in each category (therefore these figures do not add up to 203).

Sampling period: There was wide variation in the sampling schedule of the included studies, with some studies sampling for as short a period of time as one hour (Raber et al., 2011) through to studies that required samples until 24 weeks (Zhang et al., 2007, Chadwick et al., 2011). Eleven studies had an unclear sampling period or a regime that varied per individual. In 41% of studies (n= 84) the period of obtaining samples was 12 hours or less. 66% of studies required samples for a period of 48 hours or less.

Number of samples: Over all time periods the range of samples taken per patient was 1- 45, with a median of 8 samples / patient. 78% of studies (n=158) required 12 or less samples from patients.

Type of samples: The majority of PK studies sampled blood from patients (n=201, 99%). A small number of studies compared or measured PK within blood and another bodily fluid: urine (6), saliva (4) and ear effusion (1). Two studies sampled urine alone (Goren et al., 2004, Ward et al., 2005).

Language: No papers were specifically excluded on the basis of language.

3.4.2 Classification of results

There were **no** papers that reported recruitment strategies in a systematic manner (objective 1). Reporting of barriers to recruitment was variable and inconsistent (objective 2). The results which emerged have been classified into five broad categories, with a number of sub sections within each. The table of all included studies (Table 13) featured lists under which category(ies) each is eligible (final column- 'Categorised').

3.5. Results: themes

3.5.1 Recruitment

There were 38 papers in total which reported the sampling size and the number who consented or refused (see *Table 14* below). **Refusal rates ranged from 3% - 76% with a median of 41%.** Overall there was very little information provided about refusal to participate, despite the fact that studies experienced up to 76% refusal rates.

Table 14: included studies which reported consent or refusal rates

Refused	Number of identified papers	References
Reported refusal (numerical figure only)	31	Crawley et al., 2000, Wu et al., 2004, Daw et al., 2005, Broniscer et al., 2007, Horton et al., 2007, Fouladi et al., 2007, Kulkarni et al., 2007, Gururangan et al., 2008, Standing J., 2008, McGregor et al., 2009, Beaty 3rd et al., 2010, Fouladi et al., 2010, McKibbin et al., 2010, Aplenc et al., 2011, Berg et al., 2011, Warren et al., 2011, B

		Varendi et al., 2012, Blaney et al., 2013, Glade et al., 2013, Kilburn et al., 2013, Stricker et al., 2013, Hummel et al., 2013, Macdonald et al., 2013, Muscal et al., 2013, Kimberlin et al., 2013, Zorzi et al., 2013, Hiruy et al., 2014, Kim et al., 2015, Kilburn et al., 2015, Stricker et al., 2015, Young et al., 2015
Reported refusal with additional information	7	Carlsson et al., 1997, Agertoft et al., 1999, Conway et al., 2004, Dupuis et al., 2006, Kokki et al., 2006, Altcheh et al., 2014, McGregor et al., 2012
Total	38	

In 31 / 38, this was the only detail provided. Of the 7 papers that provided any further information about refusal, 3 specifically stated that there were issues related to blood sampling or the placement of an IV cannula (Agertoft et al., 1999, Conway et al., 2004, McGregor et al., 2012). One paper (Dupuis et al., 2006) reported an inability to recruit based on parents' unavailability or the patients themselves declining assent. One paper reported refusal due to not wanting to change medication regime (Carlsson et al., 1997) and two studies referred to the burden of additional hospital visits (Kokki et al., 2006, Altcheh et al., 2014). Amongst the studies reporting recruitment rates, 58% (n=22/38) involved a chemotherapy agent. This could reflect improved reporting amongst this group of medications, although with reporting rates so poor it is difficult to draw conclusions.

3.5.2 Drug administration /delivery problems

There were 52 papers which reported issues associated with drug administration or delivery in Children and Young People (CYP) (see *Table 15* below). These results were classified into those where there was an error in the dose delivered, non-adherence or an issue with the formulation and dose-delivery failure.

Table 15: included studies which reported drug prescription, administration and delivery problems

Factor	No. of identified papers	References	Scale
Bi: Drug dosing error	21	Kinney et al., 1991, Gremse et al., 2002, Best et al., 2003, Howell and Patel, 2003, Lebovitz et al., 2004, Bergshoeff et al., 2005, Lynn et al., 2007, Quinn et al., 2007, Beghetti et al., 2009, Hahn et al., 2009, Pollock et al., 2009, Saez-Llorens et al., 2009b, Gururangan et al., 2010, Knoderer et al., 2011, Piper et al., 2011, Kiser et al., 2011, Warren et al., 2011, Jimenez et al., 2012, Manitpisitkul et al., 2013, Salzer et al., 2013, Musiime et al., 2014	**0.7-12%, median 3%**
Bii: Non-adherence/Formulation issue	29	Reed et al., 2001, Capparelli et al., 2005, Chien et al., 2005, Kyllonen et al., 2005, Ward et al., 2005, Dupuis et al., 2006, Johansen et al., 2006, Kokki et al., 2006, Simpson et al., 2006, Standing J., 2008, Chadwick et al., 2009, Blumer et al., 2010, Kimberlin et al., 2010, Chadwick et al., 2011, Kiser et al., 2011, Rakhmanina et al., 2011, Warren et al., 2011, Drover et al., 2012, Fillekes et al., 2012, Oudijk et al., 2012, Malhotra et al., 2012b, Kilburn et al., 2013, Walson et al., 2013, Vrooman et al., 2013, Bunupuradah et al., 2014, De Bruyne et al., 2014, Garcia et al., 2014, Musiime et al., 2014, Zongo et al., 2014	**1-23%, median 5%**
Biii: Equipment failure	6	Agertoft et al., 1999, Stewart et al., 2004, Abdel-Rahman et al., 2008, Hammer et al., 2008, Norman et al., 2012, Weinstock et al., 2013	**1-19%, median 4%**
Total	52 papers	Kiser et al (2011), Warren et al (2011), Zongo et al (2014), Musiime et al (2014) in two categories	**0.7-23%, median 4%**

Drug dosing: 21 studies reported that incorrect doses had been administered, which meant blood samples had to be disregarded and excluded from the study. In the papers that recognised and reported this problem the problem ranged from 0.7% to 12% with a median

of 3%. PK studies are dependent on accurate prescribing and administration and errors lead to loss of participants' data.

Non-adherence / formulation issues: 29 papers reported problems related to adherence to the medication regime or problems associated with the formulation utilised within a study. These could reflect vomiting, spitting medications out or expulsion of rectally administered medications. Seven studies reported participants being unable to ingest the medication under investigation, because they were unable to swallow the tablets (Ward et al., 2005, Johansen et al., 2006, De Guchtenaere et al., 2011, Warren et al., 2011, Kilburn et al., 2013, Musiime et al., 2014) or because the route of delivery was too challenging (Kokki et al., 2006). Overall issues associated with tolerance and compliance led to researchers having to disregard data from 1%- 23% of recruited participants, (median of 5%) due to large variation in the results.

Drug delivery: Six studies reported a pump delivery problem that affected 1 – 19% of participants, with a median of 4%. If the drug fails to be delivered then the pharmacokinetic measurements have the potential to be misleading and lead to participant data being withdrawn.

3.5.3 Obtaining samples

The most common problem cited within the published literature was that of issues associated with obtaining the required samples (n=112). See *Table 16* for a full list of these studies.

Table 16: included studies which reported problems associated with sampling

Factor	No. of identified papers	References	Scale
Sampling problems	112	Saxen et al., 1993, Husson et al., 1994, Blumer et al., 1995, Force et al., 1995, Malinovsky et al., 1996, Reed et al., 1996, Birmingham et al., 1997, Carlsson et al., 1997, Geiduschek et al., 1997, Gorodischer et al., 1997, Mendelsohn et al., 1997, Reynolds et al., 1997, Stevens et al., 1997, Wintermeyer et al., 1997, Lindsay et al., 1998, Crawley et al., 2000, Hahn et al., 2000, Kearns et al., 2000, Nahara et al., 2000, Scheepers et al., 2000, Stevens et al., 2000, Wulf et al., 2000, Johnson et al., 2001, Reed et al., 2001, Ross et al., 2001, Dsida et al., 2002, Furman et al., 2002, Guay et al., 2002, Gremse et al., 2002, Orenstein et al., 2002, Lipman et al., 2002, Best et al., 2003, Fraaij et al., 2003, Kearns et al., 2003b, Sallas et al., 2003, Fletcher et al., 2004., Goren et al., 2004, Lebovitz et al., 2004, Neville et al., 2004, Oliver et al., 2004, Wagner et al., 2004, Wheeler et al., 2004, Chalkiadis et al., 2005, Jacobs et al., 2005, Saul et al., 2005, Bomgaars et al., 2006, Cormack et al., 2006, Dupuis et al., 2006, Fouladi et al., 2006, Heresi et al., 2006, Johansen et al., 2006, Kokki et al., 2006, Mehta et al., 2006, Muller et al., 2006, Zuppa et al., 2006, Aman et al., 2007, Broniscer et al., 2007, Kulkarni et al., 2007, Lynn et al., 2007, Veal et al., 2007, Abdel-Rahman et al., 2008, Bomgaars et al., 2008, Danne et al., 2008, Glade Bender et al., 2008, Gururangan et al., 2008, van Ommen et al., 2008, Neville et al., 2008, Almenrader et al., 2009, Baruchel et al., 2009, Hahn et al., 2009, Nielsen et al., 2009, Jacquemin et al., 2009, Pollock et al., 2009, Saez-Llorens et al., 2009a, Standing et al., 2010, Fouladi et al., 2010, Su et al., 2010, Chadwick et al., 2011, Forbes et al., 2011, King et al., 2011, Kiser et al., 2011, Lynn et al., 2011, Mugabo et al., 2011, Rakhmanina et al., 2011, Warren et al., 2011, Wigal et al., 2011, Chamberlain et al., 2012, Drover et al., 2012, Malhotra et al., 2012a, Autmizguine et al., 2013, Cohen-Wolkowiez et al., 2013, Demirjian et al., 2013, Glade et al., 2013, Kim et al., 2013,	**0.3-80%, median 10%**

	Kimberlin et al., 2013, Manitpisitkul et al., 2013, Min et al., 2013, Shah et al., 2013, Smith et al., 2013, Sugita, 2013, Veal et al., 2013, Vrooman et al., 2013, Walson et al., 2013, Weinstock et al., 2013, Oualha et al., 2014, Desai et al., 2014, Ramos-Martin et al., 2014, Kukulka et al., 2014, Bradley et al., 2014, Musiime et al., 2014, Woloszczuk-Gebicka et al., 2014, Hahn et al., 2015, Munoz et al., 2015, Young et al., 2015a	

Sampling problems were referred to in a number of ways within the published literature. For some studies this was reported as *'incomplete'* sampling, for example Bradley et al. (2014) reported 5/24 participants had incomplete sampling and were excluded from analysis. Other studies reported *'Intravenous catheter malfunction'*, (Drover et al., 2012) or '*vascular access unavailable'* (Mendelsohn et al., 1997). *'Insufficient sampling volume'* was referred to by some authors; e.g. 7/100 participants had insufficient blood volume withdrawn (Mugabo et al., 2011). Several studies also highlighted patients' results having to be excluded because of '*incorrect sampling*'. These included samples not being collected (Zuppa et al., 2006), being taken on the wrong day (Pollock et al., 2009) or being taken from the wrong place (Abdel-Rahman et al., 2008). The significance of sampling errors / problems varied significantly within the literature, ranging from a loss of 0.3% - 80% of participants, (median of 10%). The study which reported a loss of 80% of participants, found 16/20 patients had missing samples at 18 hours because of blood sampling issues (Woloszczuk-Gebicka et al., 2014). Overall although sampling and obtaining PK samples with CYP was identified as challenging, it was difficult to determine which aspect was the most challenging aspect due to the variance in reporting.

3.5.4 Processing problems

34 studies reported problems associated with the processing of samples and obtaining results. These problems were classified as clerical, technical and those associated with storage and transportation (see *Table 17* below).

Table 17: included studies which reported processing problems

Factor	No. of identified papers	References	Scale
Di: Clerical errors	16	Stevens et al., 2000, Tod et al., 2001, Lipman et al., 2002, Marina et al., 2002, Aquino et al., 2004, Chien et al., 2005, Diaz et al., 2007, Zhang et al., 2007, Hahn et al., 2009, Nielsen et al., 2009, Musiime et al., 2010, McJunkin et al., 2011, Piper et al., 2011, Cohen-Wolkowiez et al., 2012b, Salzer et al., 2013, Ramos-Martin et al., 2014	**1-44%, median 5%**
Dii: Technical failure	14	Blumer et al., 1995, Reed et al., 1996, Gorodischer et al., 1997, Crawley et al., 2000, Hahn et al., 2000, Ross et al., 2001, Rongkavilit et al., 2002, Fouladi et al., 2007, Gururangan et al., 2008, Malloy et al., 2009, McGregor et al., 2009, Beaty 3rd et al., 2010, McKibbin et al., 2010, Raber et al., 2011	**2-54% Median 12%**
Diii: Incorrect storage / transportation	4	Gremse et al., 2002, Fouladi et al., 2006, Bomgaars et al., 2008, Kiser et al., 2011	**1.5-25% Median 6%**
Total	34	0 papers in more than 1 category	**1-54% Median: 7.5%**

Di. Clerical errors: 16 studies reported issues associated with documentation of sample collection times or conflicts between dosing history and the recorded samples' collection times. The number of samples affected by documentation problems was not large (median of 5% amongst the 16 studies which reported problems. However, it does highlight an

avoidable problem that researchers need to address to ensure that samples taken for research purposes are handled and labelled appropriately.

Dii. Technical failure: 14 studies were classed as experiencing 'technical issues'. These included mishandling of serum and saliva (Hahn et al., 2000), improper sample preparation (Beaty et al., 2010) and difficulties with the assay (Ross et al., 2001). Reed et al (2001), highlighted that **all** of the data from the first 9 patients / 29 were invalidated after interfering substances were discovered in the stopper of the blood collecting tubes. This highlights that when there are technical issues they can have a sizeable impact on the results obtained.

Diii: Storage and transportation: 4 studies reported a loss of samples due to storage or transportation issues, affecting a median of 6% of samples to be lost from analysis. This could have a profound impact on the results if there is a lack of systems in place to detect these issues.

3.5.6 Withdrawal

43 studies reported loss of participants due to withdrawal and loss to follow up and therefore did not complete the study they were recruited to (*Table 18* below).

Table 18: included studies which reported consent withdrawal

Factor	No. of identified papers	References	Scale
Consent withdrawn	43	Fritz et al., 1994, Gaedicke et al., 1996., Canafax et al., 1998, Peytchev and Chakova, 1998, Agertoft et al., 1999, Findling et al., 1999, Crawley et al., 2000, Dallas et al., 2000, De Wildt et al., 2003, Rahman et al., 2002, Rongkavilit et al., 2002, Best et al., 2003, Fraaij et al., 2003, Gajjar et al., 2003, Conway et al., 2004, Quinn et al.,	**0.7-100%** **Median 8%**

	2004, Wu et al., 2004, Chien et al., 2005, Jacobs et al., 2005, Dupuis et al., 2006, Rodriguez-Galindo et al., 2006, van der Lee et al., 2006, Zhao et al., 2006, Almeida et al., 2008, Findling et al., 2008, Goto et al., 2008, Gururangan et al., 2008, Baruchel et al., 2009, Gonzalez et al., 2009, Chadwick et al., 2011, Lynn et al., 2011, Ademisoye et al., 2012, Chamberlain et al., 2012, Gore et al., 2013, Kimberlin et al., 2013, Thompson et al., 2013, Altcheh et al., 2014, Boddy et al., 2014, Musiime et al., 2014, Thompson et al., 2014, Wagner et al., 2004, Kukulka et al., 2014, Zongo et al., 2014, Young et al., 2015

Consent withdrawal: Withdrawal rates ranged from 0.7-100% of participants withdrawing consent for studies, (median of 8%). The study that reported 100% withdrawal of consent included seven participants, none of whom had their 48 hour blood sample taken as permission was withdrawn (Baruchel et al., 2009). Unfortunately, no further explanation was provided so the aspects surrounding this attrition are unknown. The highest withdrawal after this study was reported to be 33% (Dallas et al., 2000) so it would appear unusual for 100% of participants to withdraw from a study. Similar to the reporting of recruitment to pharmacokinetic research there is little detail *why* parents withdrew consent for their child to participate. 28 / 43 reports reported only a numerical figure on how many parents withdrew or how many patients were lost to follow up, with no further information to explain this loss. Of the 15 studies where information was provided, the biggest issue identified was that of blood sampling requirements (11/15) and extra clinic attendance (4/15), the same factors which gave rise to concerns about recruitment.

Table 19 below provides a summary of the results from each theme. Overall, sampling problems were the most common barrier reported, however recruitment problems had the greatest impact with the loss of approximately 41% of participants.

Table 19: summary: studies which experienced loss of participants'/ participants' data (by theme)

Category	Number of studies	Range	Median
A: recruitment (refusal rates)	38	3-76%	41%
B: medication	52	0.7-23%	4%
C: sampling	112	0.3-80%	10%
D: processing	34	1-54%	7.5
E: withdrawal	43	0.7-100%	8%

The key barriers identified from the scoping review are summarised in *Table 20* below. No papers identified facilitators to PK research.

Table 20: summary of barriers and facilitators (scoping review results)

	Barriers	Facilitators
Recruitment	Refusal Additional blood sampling / vascular access Additional hospital attendance Lack of published detail about recruitment / refusal	X
Medications	Drug dosing error Non-adherence to medication regime/ formulation issues Equipment failure / delivery failure	X
Sampling	Inadequate / incomplete / insufficient sampling	X
Processing	Clerical errors Technical failures in the process of sample analysis Incorrect storage / transportation	X
Outcomes	Consent withdrawn Lack of published detail about withdrawal / loss to follow up	X

3.6 Discussion

3.6.1 Facilitation strategies

The primary objective of the review was to identify and quantify strategies to improve PK trial recruitment and **no** papers reported this information. This finding was disappointingly low; however, this seems in keeping with current understanding about successful trial

recruitment. A study which explored the outcomes of Medical Research Council (MRC) and Health Technology Assessment (HTA) funded trials found only 55% of studies recruited to their target sample size and 45% needed an extension of time and / or funding (Sully et al., 2013). A US study found a third of trials at one centre (260 trials) recruited zero or only one participant at a cost of $1 million (Kitterman et al., 2011). Understanding more about strategies that improve recruitment has therefore in recent years come to be recognised as important. Research in this area is emerging but even where research has been undertaken there are very few interventions which have evidence to support a claim for increasing recruitment to trials (Treweek et al., 2010). This Cochrane review focused on the quantitative impact of measures to increase recruitment but a newly registered qualitative synthesis is suggesting that alongside this there is also a requirement to explore how potential and actual trial participants and trial recruiters perceive and experience interventions (Houghton et al., 2017). In summary, whilst there is clearly a need to understand more about facilitation strategies for paediatric pharmacokinetic research, quality research into this area has yet to be conducted. Where the scoping review was able to add more insight was into the situation surrounding barriers to PK research.

3.6.2 Barriers to pharmacokinetic research

203 studies were included within the scoping review which quantified and described problems in the conduct of pharmacokinetic studies. It therefore appeared that elucidating the barriers to conducting PK research was better-reported. This was reflected in expert review papers and commentaries which highlight that conducting PK research with CYP is a challenging area to research (Smyth, 2001, Baber, 2005, Kemper et al., 2011). Anderson et al (2007) recognised that the material reported in a paediatric pharmacokinetic publication

often did not include the tribulations endured by the authors during the study. These problems and pitfalls are therefore repeated by others in further paediatric studies and are rarely reported. Indeed their own publications surrounding trials of Ketamine (Herd and Anderson, 2007) and Clonidine (Potts et al., 2007), feature no reference to the issues of recruitment, blood sampling & laboratory handling which are referred to in their review paper (Anderson et al 2007). Reasons for this are unclear. A recently published systematic review examined the invasiveness of PK studies in CYP confirms the lack of change in PK research practice (Altamimi et al., 2016). Increasing numbers of PK studies are being conducted which is encouraging. However, reporting is inconsistent, often results are not reported for different age or weight groups and despite the rise of population PK methods, there was no change in the overall volume of blood being collected from patients over a four decade period (Altamimi et al., 2016). It is essential that problems and pitfalls researchers experience are identified to allow the identification of appropriate strategies to tackle them appropriately. Although reasons for this are unclear, the lack of transparency in reporting is likely to be a factor in perpetuating study design issues.

3.6.3 Recruitment and study retention

With 41% (median) of patients declining to participate and 8% (median) withdrawing from a PK study, the most sizeable challenge to undertaking PK research in paediatrics related to recruitment and retention. Despite the magnitude of this problem there is very little information to inform researchers why parents refuse consent to participate or withdraw from a study. Current reporting makes it extremely difficult to determine whether all patients were approached, how many declined and if so why they declined. Only 7 /38 studies (Carlsson et al., 1997, Conway et al., 2004, Agertoft et al., 1999, Kokki et al., 2006,

Dupuis et al., 2006, Altcheh et al., 2014, McGregor et al., 2012) provided any further insight into the factors that influenced recruitment. These reflected blood sampling requirements (n=3) or additional visits (n=2). This is supported by literature which highlight parents' refusal because of additional venepuncture or capillary sampling (Dlugos et al., 2005, Anderson et al., 2007, Jenkins et al., 2009). Berg et al (2010) identified that the most common reasons for not participating with a PK study (amongst 50 participants) were the requirement for extra time at hospital and requirement for an extra cannula, similar to the findings from the scoping review. Participants within this survey were a mix of adult subjects, 4 adolescents and 38 parents of children in a phase one oncology study and there was no separation of paediatric responses from the adult participants, therefore the study was excluded from the scoping review (as per the exclusion criteria in *Table 12).* The study reported that 36/ 50 participants had consented to an optional PK study (consent rate of 75%). This figure seems higher than the median found within the scoping review of 59%, however, this could reflect the fact that the survey was conducted in the context of a phase 1 oncology study, where there are often no further treatment options. This has been linked to higher rates of enrolment (Kim et al., 2008, Kim et al., 2009). Only 15 papers included any information about why participants withdrew from research and again the commonality was related to blood sampling requirements (11) or extra visits (4). Researchers cannot ignore the fact that parents find blood sampling extremely stressful and it features highly in the decision about whether to participate and whether to continue in a study. Few trialists describe how they overcome recruitment barriers and this reporting needs to improve if future research is to demonstrate increased accrual and reduce attrition (Shilling et al., 2011, Tishler and Reiss, 2011). In addition, reporting of the patient journey, including the number

of eligible patients, the number invited to participate, those who refuse and those who were included is important to describe the characteristics of those who participate. This is recognised within several reporting standards such as the Consolidated Standards of Reporting Trials (CONSORT) (Moher et al., 2001b, Schulz et al., 2010) and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (Vandenbroucke et al., 2007). There should also be sufficient information reported about withdrawals and intention to treat analysis to allow assessment of attrition bias. According to one of the widest used quality assessment scales (Jadad et al., 1996), this should not only include the number of patients lost or excluded but also the reasons for the exclusion. This is poorly described within the published PK literature currently.

3.6.4 Sampling problems

The largest volume of problems reported by published PK trials related to obtaining sufficient sample numbers and volume from participants at the correct time points. This problem meant a number of participants' data had to be excluded (median 10%). Since 99% of the studies involved blood sampling it can be reasonably concluded that most of the problems experienced occurred in obtaining paediatric blood samples. The challenge of obtaining blood samples from CYP is recognised within paediatric literature (Kauffman and Kearns, 1992, Becht and Anderson, 1996, Jenkins et al., 2009) . However, there was a lack of published details about the sampling techniques utilised which makes further interpretation challenging. Papers often did not state where blood was sampled from, whether it involved an indwelling intravenous catheter, the location of the line, the type of line utilised, the proximity of the line to the drug administration, whether the line lasted for the whole study duration or needed to be replaced, the volumes of blood taken and even the sampling

regime was not always explicitly stated. This was confirmed in a study which found 32% of published studies did not state the method of blood sampling (Altamimi et al., 2016). Without this detail, it is difficult to determine strategies that contribute to obtaining any required study samples.

A small number of studies featured non blood sampling, usually in the form of urine (Findling et al., 1999, Kearns et al., 2000, Goren et al., 2004, Ward et al., 2005, Muller et al., 2006, Bomgaars et al., 2008, King et al., 2011, Smith et al., 2013) or saliva (Gorodischer et al., 1997, Hahn et al., 2000, Aman et al., 2007, Weinstock et al., 2013). There are suggestions from the literature that non-blood sampling can be appropriate and useful in paediatric patients to avoid the use of blood sampling (Jenkins et al., 2009, Wells et al., 2009) however there is a lack of qualitative review of participants' views on this. Few studies have also undertaken paired PK readings to compare the accuracy of non-blood alternatives so the feasibility of this type of analysis is unknown for many medications.

3.6.5 Processing issues

Overall there were the fewest reports concerning processing problems (n=34 studies). However, there were cases where problems affected up to 54% of participants' data (Malloy et al., 2009) which has a huge impact on the results and conclusions of studies. Although the issues encountered were specific to the individual studies, it highlights the importance of ensuring that researchers have done sufficient preparatory work to establish stability, the process of sample preparation and development of the assay and have produced clear guidance on storage and transportation of samples. Processing relies on the administration of a known dose, at a known time which can be a major limitation in the clinical setting since the dosing regimen the patient receives does not necessarily coincide precisely with the

prescribed regimen. Documentation of the **exact** time of administration and of sampling is of paramount importance otherwise the observed and predicted concentrations could become quite discrepant (Brundage et al., 2004). The same degree of rigour must be addressed to the data recording as would be demanded in a more traditional clinical research study.

3.6.6 Reporting

The main difficulty the review encountered was the lack of detail that was included within PK publications on the conduct of the study. In other types of study design there are clear published standards for reporting results, such as the Consolidated Standards of Reporting Trials (CONSORT) (Schulz et al., 2010) or STrengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Von Elm et al., 2007) which enable the reader to determine participant flow at all stages of the trial. Guidelines and checklists help to improve the transparency and presentation of studies and therefore have the potential to improve the impact and implementation of scientific research (PLOS Medicine Editors, 2013). Evidence suggests that adoption of guidelines is associated with improvements in the quality of trial reports (Moher et al., 2001a). This review found it difficult to determine in much of the published PK literature the total eligible population screened, the proportion of these successfully recruited to a PK study and the number who successfully completed the study. This situation requires urgent attention so that readers can follow what was planned, what was done, what was found and what conclusions were drawn and assess the research critically.

3.7 Limitations of the review

3.7.1. Type of review

Although the initial intention was to conduct a systematic literature review, recognising this as being at the top of the hierarchy of evidence (Khan et al., 2003), this was not felt to be appropriate in this subject area. Systematic reviews generally recommend ensuring the trials included are of the highest quality and most recommend inclusion only of RCTs (Egger and Davey Smith, 2001, Juni et al., 2001). Randomisation is not appropriate for PK studies, which often take place in the context of phase 1 and 2 trials. In fact, only 15% of the studies within the review took place in the context of an RCT. If all other study methods were excluded there would have been little to inform the review. A decision was made by the researcher to include all levels of evidence and generate understanding of the current situation surrounding PK studies, rather than to state that no evidence was available (Ogilvie et al., 2005). Conclusions are based on the best available evidence, but caution is advised against over-interpreting the incidence data related to specific barriers to PK research.

3.7.2 Search terms

Refining the search terms to capture recruitment, barriers to study completion and retention to a study was challenging. Recruitment captured aspects associated with agreeing to participate with research but aspects related to participant retention within a study were more difficult. Initial scoping searches found retention was sensitive within psychology studies, but less so in clinical trials and participation tended to be utilised more within consumer involvement work. Loss to follow up was also not a MeSH term and proved to be a very insensitive term for papers of interest. Conclusions from the scoping review are therefore focused on barriers to recruitment, although aspects associated with retention have been identified during these searches. Limited conclusions can be drawn about

barriers to study retention specifically because the search strategy was challenging to refine. Despite the difficulties in defining sensitive terms, screening on title and abstract appeared to be effective in screening out irrelevant papers because only 12% of those reviewed in full were ineligible on population (Adult study, n=12), or on study design (not PK study, n=104) (123/1026 papers reviewed in full). Most importantly most papers were excluded on the basis that they did not experience or report any difficulties with recruitment of participants or did not acknowledge the loss (n=610). This information would not have been known without reviewing the full paper. The search strategy therefore did highlight relevant papers; however, this highlights the challenges in finding the information of interest to this review.

'Neonate' (which is defined as the first 28 days of life) was not included within the search terms. The initial scoping searches indicated 'infan*' was sensitive to studies relevant to the neonatal period. Studies which specifically stated they recruited neonates (n=13) were captured within the review, therefore papers relevant to this population were identified.

Pharmacokinetics as a MeSH term was operational from 1988. However, searches were conducted from 1990 onwards. It is therefore acknowledged that the search strategies would have been better to have extended to 1988. The paper by Altamimi et al. (2016) provides confirmation that searching before 1976 yields 0 papers. In addition 91% of papers came from 1985 onwards, but for completeness searches will be conducted for this period when the work is written up for publication.

3.8 How does the scoping review address the gap in knowledge surrounding pharmacokinetics?

The scoping review is the first review the researcher is aware of to appraise systematically the published paediatric literature and address questions associated with recruitment to

pharmacokinetic research. However, no papers identified methods to improve recruitment to PK studies. The gap in knowledge surrounding facilitators to recruitment therefore continues. The review has however addressed the gap in knowledge surrounding the barriers to PK research conduct. From 203 papers, there is evidence that 41% of approached CYP will not consent to PK research and a further 8% will withdraw from the study. The predominant reason for both non-recruitment and attrition appear to be due to the requirements associated with blood sampling and additional visits to hospital. However large numbers of studies also experience loss of data due to issues associated with the practicalities of venous access and blood sampling. This is the first account to provide a sense of scale to the problems researchers can encounter with PK study conduct at all stages. The participant data loss identified has huge implications for researchers seeking to ensure they recruit to time and target. With this knowledge researchers can ensure they set realistic targets as well as optimise their trial design by consideration of problems at all stages of research conduct.

3.9 Conclusion

The scoping review was undertaken to address the gap in knowledge associated with the conduct of PK studies. Despite wide inclusion criteria and over 4000 studies being identified by the search strategies there were no studies which reported strategies to improve recruitment to paediatric PK studies. Studies were included within the review based on reported problems associated with the conduct of PK studies; the most common issue appeared to relate to blood sampling, but the biggest challenge related to recruitment. Understanding more about the barriers to recruitment is essential as many studies fail to recruit their target sample size, or are discontinued early (Sully et al., 2013, Kasenda et al.,

2014, Pica and Bourgeois, 2016). Understanding the perspective of potential study participants and those who conduct PK research was therefore identified as essential and contributed to the development of Chapters 4-8. This is the first review, to the researcher's knowledge, to explore paediatric pharmacokinetic research and quantify and systematically categorise the barriers that exist with trial conduct. This is essential if strategies to improve the situation are to be developed.

Chapter 4: patient and public involvement and engagement in the design and development of the PRESCRIBE study

4.1 Background

4.1.1 Definition and purpose of patient and public involvement

In the UK there has been an increasing focus on patient, public and service user involvement in health and social care policy (Staniszewska, 2009, Department of Health, 2009, Department of Health, 2010) and health and social care research (Stewart et al., 2011, Staniszewska et al., 2011a). This approach, often described as Patient and Public Involvement or PPI, is defined as research being carried out 'with' or 'by' members of the public, rather than 'to' or 'for' them. The critical feature is that they are involved in research design and process rather than as subjects in the research project (INVOLVE, 2012). Public involvement in research is founded on the core principle that people who are affected by research have a right to have a say in what and how research is undertaken(Hewlett et al., 2006, Staniszewska, 2009). The benefits of consumer involvement are that researchers are assisted to understand the human aspect through patients' experiences and expertise, knowledge of issues is more complete, good practices are validated, communication becomes more patient-friendly, the right issues are addressed and the quality, relevance and acceptability of research is enhanced (Ali, 2006, Royal College Nursing, 2007, Staniszewska, 2007, Staniszewska et al., 2011a, Brett et al., 2012). It ensures that issues which are important to consumers and therefore to health resources as a whole are identified and prioritised; it ensures that money and resources are not wasted on research of little value and it encourages consumers to push for outcomes that may have greater relevance than

those considered by professionals (Boote et al., 2002). Research regulators and a growing number of commissioners of publicly funded health research now ask applicants to describe how they plan to involve the public in their research (Telford et al., 2004, Stewart et al., 2011, Staley et al., 2012, Jones et al., 2015, Bagley et al., 2016) and researchers applying through the Integrated Research Application System (IRAS) have to state their plans for involvement (Tarpey and Bite, 2014, IRAS, 2015). The NIHR Strategy document 'Going the Extra Mile' (National Institute for Health Research, 2015a) consolidates the place of PPI as a core component of good research practice and recognises the experience of patients and service users as a fundamental and valued source of knowledge.

4.1.2 PPI with Children and young people (CYP)

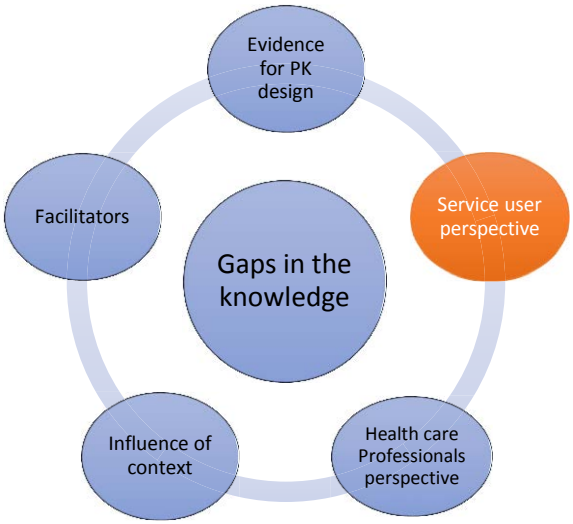
The United Nations Convention of the Rights of the Child (1989) gives children a right to be involved in decisions that affect their lives and for their views to be listened to. The principle of 'no decision about me, without me' is central to this and applies as much to children and young people as any other patient group (Weil et al., 2015). The Department of Health (2003) state explicitly that CYP should be consulted and involved in all aspects of their care, including decision making about research participation. There is a growing recognition that children have knowledge that is separate from their parents' and carers' knowledge and that this knowledge is worthy of consideration (Bird et al., 2013). This should extend to inclusion with PPI activities, to enable researchers to design studies that are more acceptable and relevant to service users themselves, not just parents (National Children's Bureau, 2010, INVOLVE, 2016a). However, despite this a recent survey of National Institute Health Research (NIHR) funded trials (2006-2010) found declining rates of PPI within paediatric trials (Gamble et al., 2014). This is of concern because conducting clinical trials in CYP is

generally regarded as more challenging than those in adults and omitting PPI could affect recruitment, appropriate design and prioritised outcomes (Caldwell et al., 2004, Tishler and Reiss, 2011, Menon et al., 2012). In paediatric studies, Research Ethics Committees (RECs) require evidence that consultation with service users has taken place to ensure that a study design is appropriate; risks and burdens have been minimised and information materials are comprehensible to their target audience (Nuffield Council Bioethics, 2015a). In the case of specific populations with serious and rare conditions, specialised input from relevant representatives becomes even more important (Nuffield Council Bioethics, 2015a). Although PPI with CYP has had a raised profile through the National Institute for Health Research (NIHR) (National Institute for Health Research, 2015c, National Institute for Health Research, 2016f) there remain few published accounts of Young Persons Advisory Group (YPAG) activities. In particular, there are few accounts of involvement within high dependency and Paediatric Intensive Care (PIC) research studies.

Although PPI has become increasingly prevalent in health service development and research, there is a gap in the knowledge about which approaches work best, when or why, or under what circumstances. Some of these uncertainties relate to difficulties with the involvement evidence base, which is relatively poor (Staniszewska, 2009). Research in this area has often been of poor quality with no specific way of evaluating the quality of PPI within a study. Also there have been difficulties attributing changes to user involvement (Crawford et al., 2002). Staley (2012) highlights that researchers' accounts of involvement have not been sufficiently detailed; often not describing the context, mechanism and expected outcome of any chosen approach. More detail is needed about where the researcher started- their original plans, priorities, values and assumptions, what recommendations were made by the public and

why, what changes were made in response and why, what outcomes were expected and what outcomes were observed by researchers and the public. This will assist researchers to understand how involvement works in different contexts and understand how outcomes are achieved (Staniszewska et al., 2008, Staniszewska and Denegri, 2013). Chapter 4 therefore aims to address the gap in knowledge related to service user perspectives in the context of paediatric PK research (see *Figure 11* below)

Figure 11: gap in the knowledge- service user perspective



4.2 Aims

1. To develop the research protocol prior to Research Ethics Committee (REC) submission in consultation with members of the public, to include:

a) Identification of the stakeholders in paediatric PK research studies (potential participants)

b) Identification of recruitment strategies for future participants (recruitment methods)

c) Identification of the methods to conduct research with future participants (methodology)

d) Identification of questions to utilise with future participants (interview schedule)

2. To develop participant information sheet (PIS) and consent / assent forms.

4.3 Method

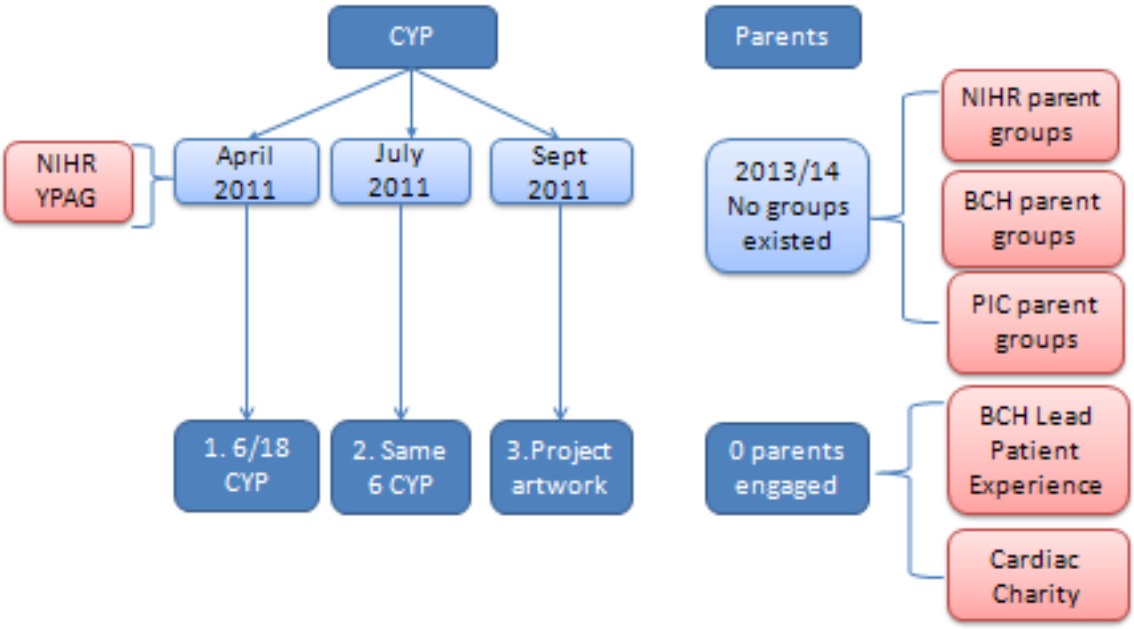
Please see chapter 2 for full details of the method. Aspects specific to identification of participants for PPI work are detailed below.

4.3.1 Participants

The plan was to work with existing service user groups, recognising that there was insufficient time, networks or resources to establish new groups of service users, specifically for the purposes of PRESCRIBE as a standalone project. These factors have been identified as barriers to involving service users (Staniszewska, 2007). Membership was conceptualised as being two core groups: children and young people (CYP) and parents. A systematic literature of public involvement in research design identified that conducting focus groups within the context of existing support groups (Boote et al., 2010) was a successful approach to follow. In light of this, existing resources were therefore sought.

Children: National Institute for Health Research (NIHR) Medicines for Children Research Network (MCRN) in the West Midlands agreed to facilitate access to an established Children and Young Person's Advisory Group (YPAG) with a remit to advise on the development and conduct of research (Dudley et al., 2015, National Institute for Health Research, 2015c, National Institute for Health Research, 2016f). The group was composed of around 18 members (8-18years) and met every six weeks. The session was planned for 26th April 2011, with participants those who attended on this day. See *Figure 12* below.

Figure 12: recruitment of CYP & parent participants for PPI work



Parents: Consultation with a group representing parents of hospitalised children was the aim, however this proved difficult to achieve. The research networks did not have a specific group of parents to advise on the conduct of research, nor did Birmingham Children's Hospital (BCH) or the Paediatric Intensive Care Unit. The Patient Experience and Participation team at BCH agreed to facilitate access to parents they had contact with but after several months of contact and negotiation this did not come to fruition (Oct 11-Jan 12). This struggle to obtain access to service users through gatekeepers is recognised as a significant barrier to PPI conduct in the literature (Smith et al., 2009). Partnership with parents who are in a similar situation to potential study participants will help to ensure that important aspects of the research question have been considered (Nuffield Council Bioethics, 2015a). However, the concept of 'similar situation' is challenging in the PIC context as patients can be 0-18years of age and there is a broad case mix of underlying diseases and diagnosis (Kleiber et al., 2015). Approximately 50% of admissions to PIC are for

children with a cardiac condition post-surgery (PICANet, 2016) and therefore parents' of children with cardiac conditions were felt to be the most representative 'group'. A local (Birmingham) Children's Cardiac Charity was approached and a session was planned with the board of the charity in November 2013. This was then rescheduled twice before this line of enquiry was abandoned.

4.3.2 Model of involvement

The involvement of consumers in research activity has been viewed on a continuum ranging from a low to a high level of activity. Consultation is regarded as the lowest level of involvement, with service-user led projects the highest (Boote et al., 2002, Staniszewska et al., 2011a). For the purposes of a single site, PhD project with no funding available for ongoing consultative approaches, consultation was felt to be the most appropriate approach. The project went through stringent peer review process in the funding application and this approach was supported.

4.4 Analysis

The plan was to use mind mapping on large A1 sheets, which would then serve as the field notes from the session. Thematic analysis and simple descriptive statistics would then be conducted. However, during session one with CYP the group struggled initially with this format. Notes were therefore made by the researcher during the session. The subsequent session was audio-recorded, transcribed intelligently (Gale et al., 2013) and analysed using thematic analysis. Participants were given a unique number and anonymised quotes are reported.

4.5 Results

4.5.1 PPI Participants

The first session was held in April 2011. Participants are summarised in Row 1, *Table 21* below. A second session had to be planned as the session ran out of time and the same six participants were scheduled for a session in July 2011. There were no changes in the constitution of the group. The third session was conducted separately to develop project artwork for the Participant Information Sheet (PIS).

Table 21: summary of PPI participants' demographic data

Date	No. participants	Age (yrs)	School Yr	Gender	Experience[1]	Method	Location of interview
April 2011	6	10-16	8-12	Male: 1 Female: 5	0-3	Focus groups: A1 paper notes for mind mapping	Wellcome Trust Clinical Research facility (WTCRF)
July 2011	6 (same)	As above	As above	As above	As above	Focus group: Audio-recorded session	As above
September 2011	8	8-16	6-12	Male: 2 Female: 6	No records	Project artwork and PIS development	As above

[1]Experience: 0= No experience, 1= visitor to hospital setting, 2= experience of outpatients / ED, 3= experience as an inpatient

4.5.2 Protocol development

4.5.2.1 Research participants

The YPAG identified six key groups with whom it was essential to engage about future PK studies. Following PPI there was a substantial increase in the stakeholder groups from the original plan (*Figure 13*) to what was actually conducted (see *Figure 14*). The purple boxes denote work PPI participants felt could be conducted, but did not take place.

Figure 13: PRESCRIBE planned research activity (pre-PPI)

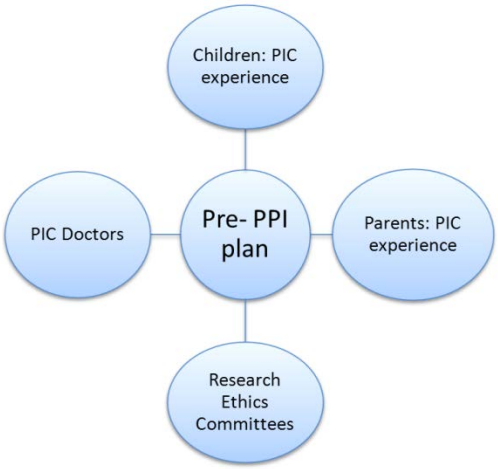
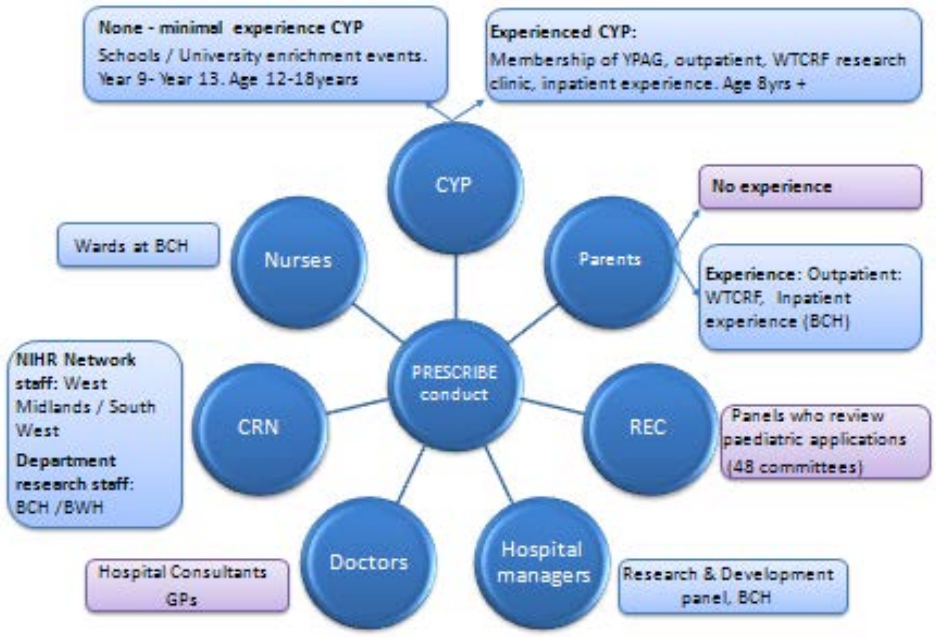


Figure 14: post-PPI research conduct for PRESCRIBE



Additional stakeholders identified were nurses, hospital managers and research personnel. In addition, consumers- CYP and parents- expanded from those with PIC experience, to those with wider hospital experience and to the lay population, in order to review the influence of experience on participants' views and attitudes. There were three key areas where the advice of the YPAG was not followed (the purple boxes on *Figure 14*)- the lay parent group,

Doctors and REC committee members. Engaging with parents connected to the hospital environment was extremely challenging and efforts were channelled in to ensuring those *with* experience of the hospital setting were recruited. After initial attempts to engage with Doctors across the Trust, the decision was made to follow this group up at a later stage. This group were challenging to engage with due to their workload and rapid changes to their availability. A survey with REC members was developed but was not conducted because of time constraints. Overall the impact of PPI was to significantly broaden our participant groups and widen the inclusion criteria for the future qualitative studies.

4.5.2.2 Recruitment methods

The YPAG identified that for health professionals and REC members, invitation to participate could be undertaken by email. See *Figure 15* below for a summary of their views on recruitment of participants. For CYP and parents however recruitment was felt to be best conducted face to face, to ensure that the timing was appropriate. Recruitment could take place in a variety of areas, provided there was sensitivity to the individual's circumstances, particularly those in Emergency Department (ED) or PIC. To capture the perspective of those with no experience of the hospital setting, they felt this work would be best conducted in the school setting.

Figure 15: planned method of recruitment for each participant group

Overall recruitment methods did not change as a result of PPI but the impact of PPI was to verify the planned approaches. These plans continued through to implementation of the research protocol.

4.5.2.3 Methodology

The planned methodology was envisaged to be focus groups. Overall this approach was supported by the PPI collaborators, with focus groups viewed as the best methodology to conduct with nurses, Research Network staff and Hospital managers. The YPAG did however caution that this could be problematic for CYP and parents, citing challenges with child care, travel and working patterns. To overcome this, they suggested discussion of preferences with participants at the time of approach, with the offer of an interview if the CYP or parent preferred (protocol amended to reflect this choice). There was a potential place for questionnaires / e-surveys, although there were recognised limitations for both methods.

The impact of PPI was to confirm the selection of methodologies for some groups and to make modifications to allow for participant choice.

4.5.2.4 Interview schedule

Key topic areas to address within the interview schedule were discussed with the YPAG, see *Table 22* below. These generated questions to be posed within the interviews or aspects they felt would need to be addressed. Examples raised are listed below in *Table 22*, along with quotes from participants. The impact of PPI was therefore in the generation of topics for discussion.

Table 22: interview topics and questions generated by PPI participants'

Group	Topic	Questions
CYP	• Type of sample • Blood sampling • Sampling regime • Risks of participation • Pain	What type? Where do you take it from? How much? What happens if they can't obtain the sample? Extra attendance at hospital? How long for? Are there alternatives? Scarring? Side effects? Safety? What happens to the samples after? Will it hurt? What can you do to minimise pain? ***"What happens if you don't bleed? Is there a maximum number of times they'll stab you?" (YPAG-4)***
Parents	As above, **plus** • Longer term effects • Commitment • Benefits of participation	How long do we need to do this for? How much extra is this to normal? Do you 'share' the results? Will this benefit care? ***"Parents might think more long term.... like what's the period of the study? How long is it going to be going on? How long are you going to want the bloods? "(YPAG-3)***
Nurses	• Time • Workload • Blood sampling • Gatekeeper • Results	How much time is required? Is there help available? What is involved? What does this mean for medications? Where do we take samples from? How many? Which patients? Is this safe for them? What happens to results? Will this change patient care?
Hospital Managers	• Invasiveness • Impact on patients • Medicines management • Cost implications	How many invasive procedures? Where will this take place? How will this affect patients? What is the impact on prescribing? Could this avoid other procedures? Are there cost savings to be made?

4.5.3 Participant Information Sheet (PIS) and study paperwork

The YPAG highlighted that they felt it was important for a study to have an identity or a logo and for this to be used consistently throughout the study. The YPAG therefore produced the prototype PRESCRIBE logo (final results produced by a graphic designer). In addition, they provided feedback on the content and readability of the PIS. The impact of PPI was the restructuring of information into shorter paragraphs, clarification of study activities and highlighting where graphics would be of benefit. Comments on the consent and assent forms reflected the need for short sentences and ensuring the language was appropriate for the age bracket for which it was designed. See *Appendix 3* for copies of PIS.

4.6 Discussion

4.6.1 Consultation

PRESCRIBE utilised a consultation approach to PPI, with engagement focused at the pre-protocol development stage. This approach has been criticised as being the lowest level of PPI engagement, with participants often passive in the research process (Boote et al., 2002). However, early PPI at the pre-REC submission stage is recognised as being the most credible and useful, as it optimises the impact and relevance of research (Buck et al., 2014). At this stage, many decisions are made that determine the relevance and conduct of the research question, the precise specification of the research question, methods of data collection, recruitment and consent procedures (Staniszewska, 2007, Boote et al., 2010, Brett et al., 2012). In addition, although activity is defined as *one-stage* PPI, it was not a *once-only* event. Consultation with the YPAG took place on three occasions: twice in relation to the protocol development and once in relation to the PIS and artwork. There is also a danger of PPI profligacy, the encouragement of elaborate plans for PPI that are disproportionate to the

needs of a trial (Buck et al., 2014). For the purposes of this project, consultation focused on the pre-protocol stage was felt to be appropriate.

4.6.2 Engaging with the 'right' people

Despite efforts to conduct PPI with parents who understood the PIC setting, strategies were unsuccessful. Finding and engaging with the right people with an interest in and understanding of the research is recognised as a major hurdle for researchers (Buck et al., 2014). Efforts were made to utilise existing resources within the local NHS Trust but there were challenges with Hospital gatekeepers and a reluctance to 'share' databases of parents. Many researchers conduct PPI with patients known to the researcher through clinical care (Mathie et al., 2014). In fact a study exploring PPI training with 31 researchers from 28 trials found that only one Chief Investigator sent out an advert inviting people to volunteer for the role of PPI contributor (Dudley et al., 2015). This can create challenges for researchers of managing 'known' patients and there can be issues for participants about raising aspects which imply criticism of their clinicians or services (Buck et al., 2014). Given that CYP who utilise PIC services are, by nature critically ill, it was felt inappropriate to conduct PPI with families of CYP who were current service users.

Unlike other disease-specific support groups, there are no national support groups that specifically exist for parents of former critically ill children (Menzies et al., 2016). It is therefore difficult to reach and engage with parents in the design and conduct of trials carried out in the PICU environment. Tume et al (2015), despite using a variety of recruitment strategies locally and nationally over a 6 month period, were only successful in engaging in PPI with two parents of children who had been PIC service users. They report that the actual consultation work was relatively straightforward but the main challenge was

in the recruitment of parents to the consultation process. This mirrors experiences of consultation with parents of children who had experienced a PIC admission for Refractory Status Epilepticus. Of 56 families approached for participation in a focus group, there were 47 non-responders and only representatives from 5 families went on to be involved in a focus group (Menzies et al., 2011). Even when the method was a telephone interview, only 35% (12/34) of parents approached agreed to participate (Agrawal et al., 2009). There is significant effort required to conduct this type of 'stand-alone' consultation, where participants are sought for a specific focused project. Within the time restrictions of a PhD project the decision was made to find an existing group of parents who already met for a specific purpose. In addition, because of the context under consideration it was decided that the group needed to have some understanding of the challenges involved with having a child admitted to hospital and being prescribed medications. This is in keeping with PPI guidance, that wherever possible, utilise existing PPI resources (Morrow et al., 2012). Social media offers new avenues and opportunities but these were limited in 2011-2012.

4.6.3 Impact: recruitment rates, documentation and approval

One of the commonly reported impacts of involvement is an increase in recruitment rates (Vale et al., 2012, Ilife et al., 2013). This is complicated because studies have often compared one group of projects with some kind of involvement, with another group of projects with no involvement, without controlling for other contextual factors that might influence recruitment (Staley, 2015). In the case of PRESCRIBE it is difficult to measure the impact because recruitment to all groups was considered within the PPI consultation and there was no other 'similar' project with which to compare it. In addition, gains provided from PPI are often diffuse and hard to quantify (Fudge et al., 2008). There was also no

particular anticipated problem with recruitment. However, recruitment as a process went smoothly and exceeded target sample size for many of the participant groups. Contributing factors were felt to be the consideration of recruitment strategies and the most appropriate methodologies for each participant group. PPI verified the planned approaches and identified new groups with which to engage. Whilst recruitment to time and target cannot be directly attributed to one factor, the care and consideration taken at the pre-protocol stages were felt to have contributed to the smooth progress of the study.

Involvement of consumers in studies has been identified as contributing to improvements in the study documentation, including protocol development and Participant Information Sheet (Vale et al., 2012, Mathie et al., 2014). This is reflected in PRESCRIBE, with contributions to PIS for parents (for CYP focus groups), CYP aged 8-10years, CYP aged 11-16years, a PIS for a parent focus group as well as consent and assent forms. Measuring the impact of these changes is again challenging but as these are key documentation reviewed by the Research Ethics Committee (REC), it can be seen as positive that there was only one additional sentence required by the REC to *any* of the study documentation.

Research Ethics Committees require researchers to demonstrate evidence of PPI activity to ensure that a study design is appropriate, risks have been minimised and information materials are comprehensible to their target audience (Nuffield Council Bioethics, 2015b). The impact of involvement is therefore that ethically acceptable research is designed and the approvals process is facilitated (Staley, 2015). Following submission, the study was approved (subject to the one amendment about the use of quotes) within six days. Whilst this cannot be fully attributed to the PPI conducted as proportionate review, an expedited

review of research studies which raise no material ethical issues (Health Research Authority, 2014) was applied for. However, the PPI work impacted on the overall standard of the application, which was felt to have facilitated the speed of approval.

4.6.4 Impact: on the researcher

Whilst PPI was planned from the outset, the value of PPI was under-estimated. A review of documented PPI plans in funding applications found this was a common fault (Buck et al., 2014). Planned PPI activity for PRESCRIBE went from being a two-hour once-only activity to help populate the protocol, to contributing to three sessions, with the development of project related artwork and logo, the development of the interview schedule and vignette as well as the details required for the protocol regarding recruitment and methodology. A thesis chapter specifically on PPI also evolved, a future publication about the conduct of PPI with CYP is drafted as well as a publication about the challenges of PPI within the PIC context (Menzies et al., 2016). De Wit et al (2014) highlight that one of the most important outcomes from involvement is the reality check for the researcher and the challenge that involvement makes to their thinking, planning, values and communication. This is equated to a form of experiential learning for researchers (Staley, 2015). One of the biggest impacts of PPI for PRESCRIBE is therefore the experiential knowledge gained by the researcher about the potential contribution of PPI through direct experience of working with the public.

4.7 How does PPI work conducted address the gap in knowledge?

The narrative review, conducted to explore PPI within the PIC setting, demonstrated the lack of published examples of PPI engagement in this context (Menzies et al., 2016). In 2016 there was only one paper which described PPI within Paediatric Intensive Care trial design

(Tume et al., 2015), rather than *research* on trial design. Researchers working in PIC are in the woeful position of having few options to guide them in their own research design and conduct. This runs the risk of perpetuating more badly designed studies or trying to answer questions which patients and their families do not view as important. Staniszewska et al (2011b) describe the current evidence base as like an iceberg, only partly visible within the literature, with much information hidden, either not reported or poorly reported. The recently published article makes the important step towards consolidating and highlighting the literature surrounding PPI in the PIC context (Menzies et al., 2016). There is also a need to understand the *impact* of PPI on any aspect of trial design (Staley, 2015). Researchers need to publish their experiences to encourage this transparency and ensure others can see the nature and value of the contribution PPI has made to the study (National Institute for Health Research, 2015a). In recognition of this, the next step is to contribute to the evidence base of PPI with CYP by developing the abstract (Menzies et al., 2013) to a full paper.

4.8 Limitations

A major limitation was the underestimation of challenges of undertaking PPI activity with parents. Navigating consumer networks and organisations can be difficult as can the process of communicating goals and intentions to gatekeepers and facilitating access to potential participants (Smith et al., 2009). In future projects, negotiation with a number of gatekeepers and the pursuit of several options simultaneously is recommended.

There were many benefits to consulting with the NIHR Clinical Research Network YPAG. They were accessible, met regularly and were well facilitated (National Institute for Health Research, 2016f). They lived locally and therefore represented service users within the local

geographical area and some were service users at the local hospital. They were also already trained to some extent in research terminology and could comprehend the concepts under debate. This is important because researchers have identified that PPI contributors should be confident, motivated, intelligent and have relevant experience (Dudley et al., 2015). However, there is a question about whether they represent the authentic patient perspective. Indeed, this difficulty of ensuring that participants are representative of the wider public is often cited (Boote et al., 2010). Within the adult PPI literature it has been identified that individuals who are educated and articulate are more likely to volunteer as PPI contributors and are also more likely to identify with the perspectives of the researchers (Enany et al., 2013). The researcher acknowledges that consulting with an existing panel of CYP with an established remit to advise on paediatric research does not ensure representation of the West Midlands CYP population but in 2011, there were very few other opportunities. The YPAG was felt to be diverse enough to represent different ages, gender, ethnicities and experiences of hospital services including high dependency areas. In addition, the group were briefed on the PIC environment by the PPI leads, including a visit to PIC to understand the context of the research studies.

The researcher was not able to take on board all the YPAG's suggestions due to the timelines of the PhD and the resources available. Guidance documents have stated that researchers must value the contribution of CYP and highlight that overlooking comments can lead to CYP withdrawing from projects (Bird et al., 2013, INVOLVE, 2016a, INVOLVE, 2016b). In line with recommendations, feedback was provided about why suggestions were rejected to demonstrate transparency in the decision making process (Telford et al., 2004, Snow et al., 2015). The YPAG reported feeling positive about the experience of consultation and future

collaboration with the researchers and this is viewed as another successful outcome of the work. Pharmacists were not identified by the PPI work as a group to engage with. The pharmacy team locally were a very small team and extremely busy, so after consideration the decision was made to not engage with this group for PPI purposes.

4.9 Conclusion

PPI conducted for PRESCRIBE contributed to improvements in the protocol design and paperwork as well as timely ethical approval. It also contributed to the researcher's knowledge and professional development and confirmed the value of PPI within paediatric research. One of the strategic goals of the NIHR is that by 2025 the evidence base for PPI will be strengthened through published accounts of what works (National Institute for Health Research, 2015a). The next step is to share the experiences of PRESCRIBE and contribute to this evidence base, highlighting the impact and value of meaningful PPI.

Chapter 5: The attitudes of school children, years 9-13 towards pharmacokinetic research

5.1 Introduction

The NHS research strategy is to improve the health and the wealth of the nation through high-quality research (Department of Health, 2006). There is evidence that patients cared for in research-active hospitals have better outcomes (Ozdemir et al., 2015), but the viewpoint of the wider public about research is still relatively under-researched. Amongst adults there are generally high levels of support for research activity (Madsen et al., 1999), particularly in the presence of major diseases (Kemp et al., 1984) or critical illness (Burns et al., 2013). Within the lay paediatric population, two notable studies were identified; one comparing attitudes towards health research of lay children compared to those with a chronic health condition (Cherrill et al., 2010) and a second reviewing the attitudes of school children towards the use of unlicensed medications (Mukattash et al., 2012). However, within paediatrics overall there very few published accounts of engagement with lay children and young people (CYP) (Hill, 2006). Patient and public involvement (PPI) consultation work outlined in Chapter 4 advised that work should be directed towards understanding the perspective of the lay paediatric population, rather than just those with first-hand experience of the hospital sector. No publications about the views of lay CYP towards pharmacokinetic research were identified within the published literature. There was an identified gap in the knowledge surrounding the service user or potential future service user perspective which this body of work set out to address (see *Figure 16* below).

Figure 16: gaps in knowledge surrounding the 'lay' CYP perspective

5.2 Aims

Utilising quantitative methods:

a. Determine the attitudes of a lay paediatric population towards paediatric PK studies

b. Identify what a lay paediatric population perceive to be barriers or problematic about the conduct of paediatric PK research studies

c. Identify what lay paediatric population identify to be enabling or facilitating the conduct of PK research studies.

For all information related to method and analysis see Chapter 2- Method.

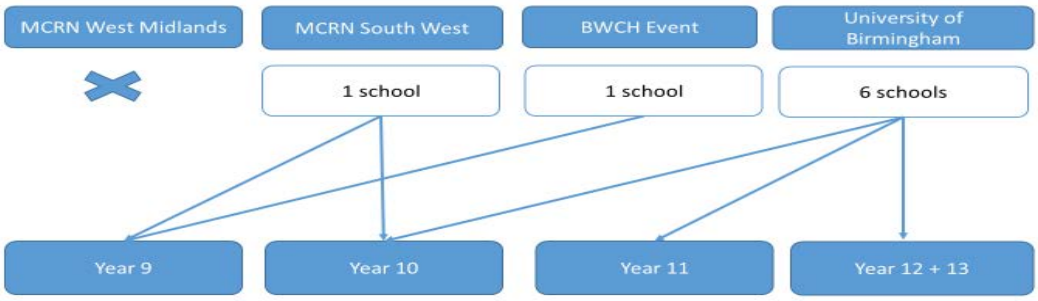
5.3 Results

5.3.1 Schools

The set up and conduct of this work was initially extremely challenging. Of three schools in the West Midlands contacted on two different occasions, there was no response from any of them. Of two further schools contacted through the South West Medicines for Children Research Network (MCRN), one did not respond after an initial expression of interest (see

Figure 17). One school was included through an event at BCH and an enrichment programme at University of Birmingham (UOB) provided access to six schools (West Midlands)

Figure 17: summary: method for how schools were accessed



5.3.2 Participants

134 participants took part in the sessions. No parents declined for their child to participate. Thirteen were 19-21 years old, and so were excluded (from the sessions at UOB). One declined to complete the questionnaire so responses from 120 participants are included within the results (response rate 99%). See *Table 23* below for details of the sessions and the number from each school year.

Table 23: summary of lay CYP recruits by school year

School year	Location	Date	No. participants
Year 9	School, West Midlands School, Bristol	Feb 14 March 14	29 (subgroups of 7-8) 22 (1 session)
Year 10	School, Bristol UOB, West Midlands[1]	Feb 14 July 14	5 (1 session) 8 (1 session)
Year 11	UOB, West Midlands[1]	July 14	18 (1 session)
Year 12 & above	UOB, West Midlands[1]	August 14	52 (sub groups of 12-13)
Total respondents			134 (120 included)

[1]Attendees were from approximately six different schools across the West Midlands

Further details about the participants are presented in *Table 24* below. The largest group of participants was students in year 9 (n=49, 42%). 14% (n= 17) of participants classified themselves as having no experience of the hospital sector, whilst 34% (n=41) reporting to

have had at least one inpatient stay (excluding birth). 25% (n=30) reported taking medications and 28% (n=34) classified themselves as having a health problem. Respiratory, skin and hay fever / immune system issues were the three highest reported problems, see *Table 24* and *Table 25* below. This correlates with their medication use with 9% (11) reporting using inhalers and 5% (6) using antihistamines.

Table 24: summary of lay participant characteristics

Characteristics	Frequency	Percentage
Gender		
Male	43	**36**
Female[1]	77	**64**
Total	120	**100**
School year		
Year 9	49	**42**
Year 10/11	29	**25**
Year 12/13	39	**33**
Total	117	**100**
Medication use[2]		
Yes	30	**25**
No	88	**73**
Unsure	2	**2**
Total	120	**100**
Medical condition		
Yes	34	**29**
No	85	**71**
Total	119	**100**
Hospital experience[3]		
None	17	**14**
Visitor	10	**8**
Outpatients / ED	52	**44**
Inpatient	41	**34**
Total	120	**100**

[1]One of the schools was a comprehensive school for girls only, all the other schools were mixed comprehensive schools.
[2]At time of completion of questionnaire
[3]Respondents' answers were coded to reflect their highest level of experience. Visitor coded as 1, outpatient/ ED visit coded as 2, Inpatient stay coded as 3.

Table 25: summary of health issues of lay participants' (self-reported)

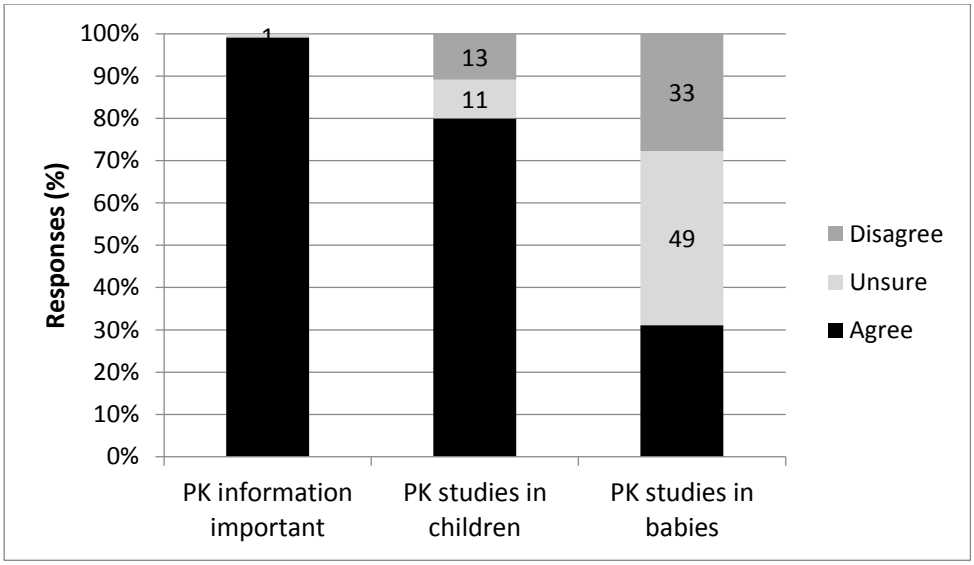
System	No.	Total	%
Respiratory[1]	11	119	9
Skin	10	119	8
Hay fever/ Immune system[2]	6	119	5
Bones / mobility	4	119	3
Blood	3	119	3
Heart	3	119	3
Hormone	1	119	1
Cancer	1	119	1
Metabolism	1	119	1
Sickle cell	1	119	1
Diabetes	1	119	1
Liver	1	119	1
Kidneys	1	119	1
Mental health	1	119	1

[1]Inhalers: N= 11 (9%)
[2]Hay fever/ antihistamines: N=6 (5%)

5.3.3 Attitude towards PK research

99% (n=119) of participants either agreed or strongly agreed that it is important that Doctors make sure they give people the right amount of medicine. This factor was found to be significantly correlated with experience of the hospital setting (p= 0.026). When asked whether this type of research should take place with CYP, the number who responded 'agree' and 'strongly agree' dropped to 80% (n= 96) and reduced to 30% (n=37) when the participants were changed to babies and young children (displayed in *Figure 18* below).

Figure 18: lay CYP views on acceptability of PK research in adult, children and infants



15% of participants made additional statements about the conduct of research with children (18/120), or babies (17/119) or both (8/119). Some made additional comments because they were *uncertain* about whether research should take place:

> *"Babies that are very, very young are likely to have a weaker immune system"*
> *('Unsure': S- 33)*

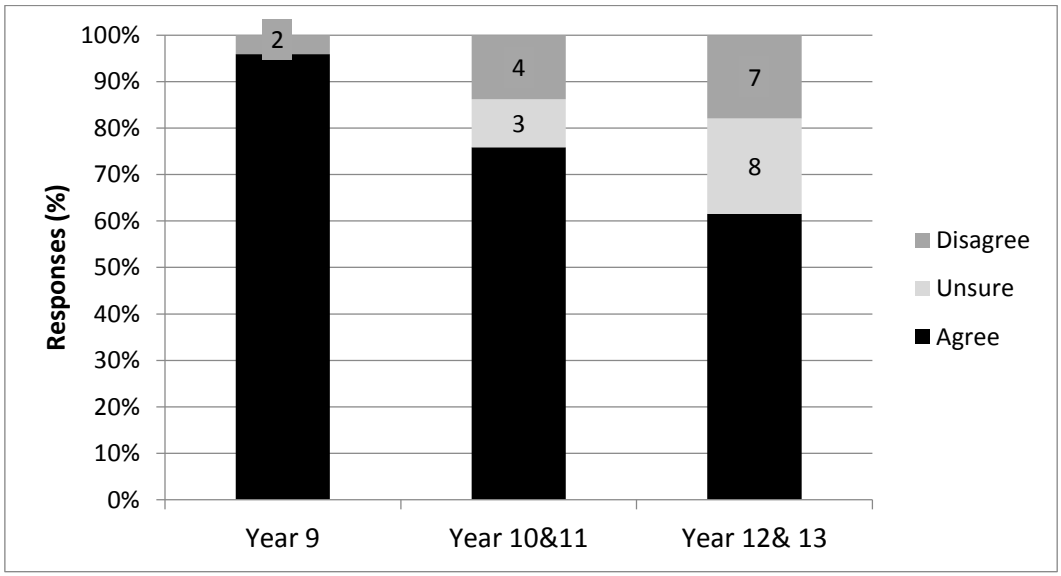
Others added clarification to statements to emphasise their reasons for *disagreeing / strongly disagreeing*:

"I think babies are too vulnerable to be tested on" ('strongly disagree' S-8)

"They can fall ill too fast" ('strongly disagree', S-22).

School year was found to have a significant association with whether research should take place in children and young people (p<0.001). Year 9 students were the most positive about this research taking place, with the level of agreement reducing as the participants got older. Post-hoc analyses found the year 12 and 13 students to have significantly lower agreement with the statement than those from either year 9 (p<0.001) or year 10/11 (p=0.040) (see *Figure 19* below).

Figure 19: lay CYP views on the acceptability of PK studies in children



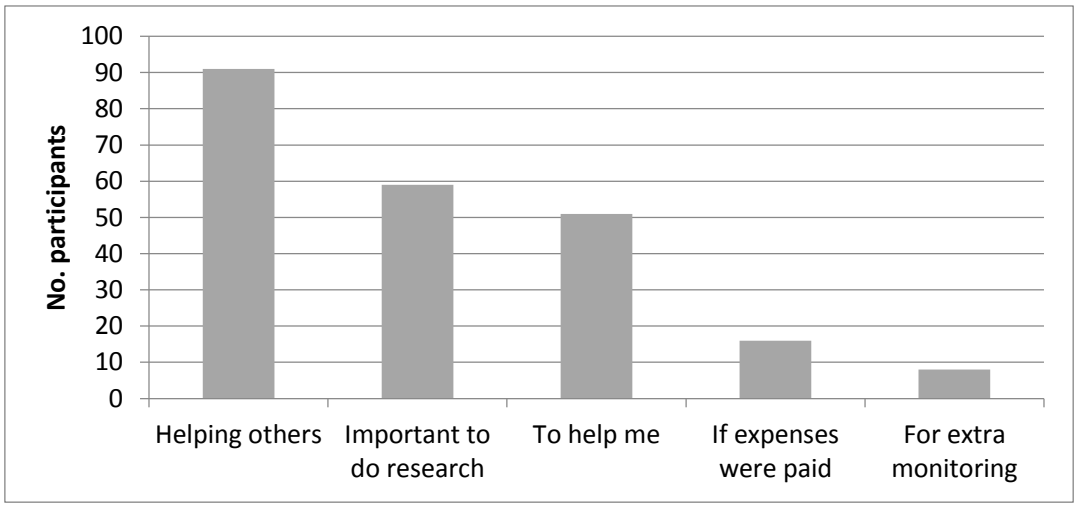
5.3.4 Participants attitudes towards personal participation

When asked about whether they would take part in the study described within the vignette (please see *Appendix 1*), only 19% (n=23) said 'No' outright. 32% (n=38) felt unsure about personal participation and 49% (n=59) said 'Yes'. Personal participation was not associated with gender, school year, medication use, health conditions or experience of the hospital sector.

5.3.5 Motivational factors for participation in a PK study

When asked about the factor(s) which would make them consider taking part in a PK study, the biggest influencing factor was to help others (76%, n= 91), followed by the belief that it is important to do research n=59 (49%) (all options are displayed in *Figure 20* below).

Figure 20: lay CYP reasons for considering participation in a PK study



Helping others was associated with a number of factors. Females were significantly more likely than males to report being motivated by helping others (84% vs. 60%, p=0.007). School year was also significantly associated with being motivated to help others (p=0.040), with the proportion of participants agreeing with this statement increasing from 67% in Year 9 to 90% participants in years 12 and 13. Increasing experience with the hospital setting was also significantly associated with the motivation to help others (p=0.002). Post-hoc analysis also found that those with experience as an inpatient were over twice as likely to be willing to help others than those with no hospital experience (88% vs. 41%, p=0.003).

5.3.6 CYP concerns about PK research and positive influences to participation

Participants were asked to identify the aspects of a PK research study that gave them concerns about participation. Their biggest concerns are listed in *Table 24* below.

Table 24: CYP concerns about participation in PK research (L) and positive influences on participation (R)

Concerns[1]	Frequency	%
Pain	74	62
Parental decision making	59	49
Personal decision making	53	44
Extra cannula	52	43
Extra bloods	47	39
Extra visits	42	35
Scarring	39	33
Understanding what is being done & why	39	33
Making extra work for staff	19	16

[1]*Participants were allowed to tick as many answers as was applicable.*

Positive influences to participation[1]	Frequency	%
Provide clear information	88	75
Ask me directly about participation	87	75
Use local anaesthetic agents	83	72
Use a central line where possible	66	56
Take smallest amount of blood	60	52
No extra visits	55	47
Use urine or saliva	51	44
Use 'leftover' blood only	48	41
Take only alongside routine bloods	38	32
Minimise extra work for staff	37	32

Pain was the highest ranked concern and was correlated with gender, with females more likely to report being worried (p=0.015) (see left side of *Table 24*). 'Parents having to make a decision about participation on their behalf' was the second highest ranked concern. Those participants with this concern (n=59) were found to be significantly more likely to report the use of medications (p=0.047), and having a medical condition (p=0.034).

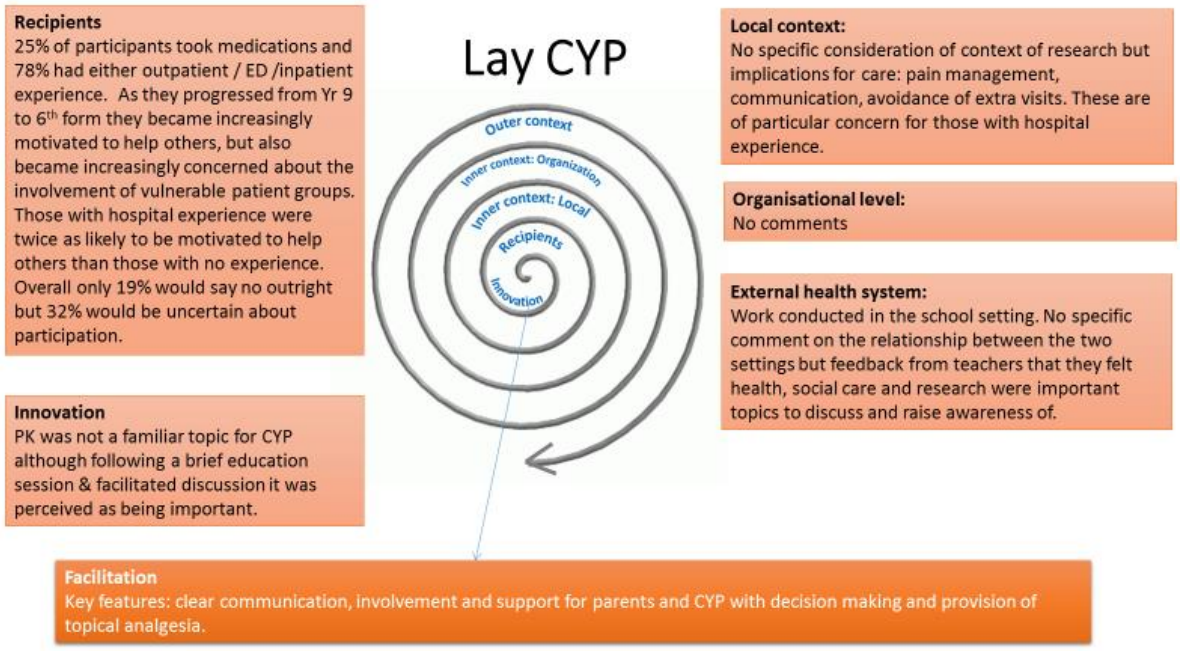
The provision of simple, clear information about the study was the highest ranked influencing factor for CYP (see right of *Table 24* above). It was significantly correlated with school year (p=0.047), with 90% (n=35) of year 12 and 13 students reporting this as an influencing factor, compared to 67% of those in year 9. Given that decision-making about participation was a significant concern it is notable that being asked directly about participation was the second highest rated facilitating factor. Using left-over blood was regarded as a positive factor for those with experience of being an outpatient (55%, n= 28) or inpatient (35%, n=14), rather than those with no hospital experience (19%, n=3)

(p=0.018). Those with hospital inpatient experience (n=22) were more likely to find 'no extra visits' important than those with no experience (n=6) (55% vs 38%) (p=0.03).

5.4 I-PARIHS

Using the integrated PARIHS framework (I-PARIHS) (Harvey and Kitson, 2016) outlined in Chapter 2, the key aspects for the 'recipients' -lay CYP- have been mapped out in relation to the 'innovation' PK research studies (see *Figure 21* below). This demonstrates that there was little consideration of context specific factors and CYP were more focused on the direct impact of research to recipients.

Figure 21: lay CYP responses mapped to I-PARIHS



5.5 Discussion

5.5.1 Participation with PK research

CYP within this study were overwhelmingly supportive of the idea of ensuring medicine optimisation. However, this support diminishes when research potentially involves younger children and infants, particularly amongst older children. This is in keeping with one of the few studies to explore school children's attitudes towards clinical trials. Within the study

conducted by Mukattash et al (2012) the general view, particularly amongst older children, was not in favour of children taking part in trials unless they were seriously ill. Concerns about vulnerability appeared to be the main reason although this could also reflect concerns that they have a right to make decisions for themselves (Balen et al., 2006).

Respondents within the PRESCRIBE study were also hesitant when they were asked about personal participation in a PK study, with 49% saying yes and 32% unsure from across all the age groups. This potential consent rate is supported by the fact that 50% of children aged 11-16 also agreed to participate in a theoretical trial to assist with the licensing of medicines (Mukattash et al., 2012). However, there is some indication that this consent rate could be higher in trials conducted with CYP with health conditions. 97.4% (n=112) of children who had participated in a trial reported they were happy about participation with the study and 91.3% (n=105) would agree to be in a future study (Fogas et al., 2001). Whilst this positivity is encouraging, this was a population PK study of steady state methylphenidate with only a single venepuncture and does not represent the requirements of many more complex PK studies.

5.5.2 Motivation

The biggest motivational factor amongst CYP was to help others; particularly for females, those with experience of the hospital setting and older CYP in school years 12-13. This is in keeping with published literature, which has found that CYP are capable of altruism (Wendler and Jenkins, 2008, Wendler et al., 2012) and that those with chronic illness might be more motivated to participate (Cherrill et al., 2007, Cherrill et al., 2010). In one of the few studies to explore attitudes towards PK studies in children with a chronic condition, self-interest was a larger motivator (47%) than altruism (39.1%) (Fogas et al., 2001). However,

only 61% of those who participated with the PK study consented to be interviewed so it is unclear if this was the motivation for all study participants. In addition, participants were interviewed over 8 months after participation so there is a question about the reliability of children's recollection surrounding their decision making. The concept of decision making about participation is hugely important and research which provides insight into this phenomenon is clearly useful. Year 9 students were the most open to inclusion of all patient groups to the research and showed a trend towards being the most likely to consent to participation (although this figure did not reach statistical significance). These differences highlight the need for approaches to consider the influence of age as well as health status. Overall the findings add weight to the notion that CYP are capable of altruistic behaviours. However, the study only included those in year 9 and above (aged 13 and over). Other published literature has similarly excluded younger children so there is a dearth of information about the perceptions of younger school age CYP. Future research therefore needs to explore this notion with a younger population. It would also seem wise to explore differences in school year as this might determine information needs and the pitch of participant information sheets (PIS).

5.5.3 Concerns and anxieties about PK research

Pain was the highest ranked concern of lay CYP in the school setting. This is supported by literature which highlighted that fear of phlebotomy is the principle reason for refusal for research (Dlugos et al., 2005) and venepuncture is the most distressing aspect of a hospital admission (Duff, 2003, Hands et al., 2010). Factors that reduce pain such as the use of topical local anaesthetic, use of a central venous line (where possible) and the use of leftover blood were ranked as positive influences by CYP within the questionnaire. These results

demonstrate that lay CYP recognised the value of approaches which reduced or avoided painful procedures, such as using scavenged samples (samples obtained without obtaining additional blood) (Cohen-Wolkowiez et al., 2012a) or the use of local anaesthetic to minimise pain (Cordoni and Cordoni, 2001).

The other big concern expressed by CYP was decision making, either their parents making decisions without their involvement or a concern about how they themselves would make decisions whilst unwell. This is validated by the fact that the biggest facilitators to PK research were the provision of clear information, particularly for older students, and being asked directly about participation. CYP indicated they wanted to be involved in the decision-making process and worried about not understanding what was required of them in a study. There is some evidence in studies with parents that a lack of experience with research heightened parents' anxiety levels (Langley et al., 2003). Another study found the more experienced parents are with science and medicine, either professionally or as a consumer of health services, the more open they are to the prospect of their child taking part in vaccine research (Chantler et al., 2007). Familiarity did not predispose to enrolment in research, but did contribute to parents' confidence in decision making, acceptance and judgement of the research. Given that the CYP in this study placed such importance on information and rated not understanding what is going on amongst their biggest concerns, this would suggest that CYP also value science and medicine and the ability to make sense of what a study requires. There is a growing recognition of the importance of beginning this education within the school setting. Education about research would contribute to enhanced awareness and understanding about research amongst a lay population of CYP

(National Institute for Health Research and GenerationR., 2014, National Institute for Health Research, 2015c).

5.5.4 Experience and health status

Those with experience of health care settings were more likely to be motivated to help others; with those had been an inpatient over twice as likely to be motivated than those with no hospital experience. Cherrill et al (2010) similarly found CYP with a chronic illness were more likely to support children's involvement in clinical trials than those without. CYP in PRESCRIBE with inpatient experience were also more likely to regard having to attend hospital for extra visits as a negative influence on their decision making and rated the use of approaches which utilised leftover blood samples. Health status appears to have a large influence on CYP decision-making, however this is challenging to capture in a non-health care setting. Within the questionnaire CYP reported medication use at 25%, and the presence of a medical condition in 28%, which seems in line with the estimate of 31% of children are affected by a chronic condition (Newadreck & Taylor 1992). Other studies conducted within the school setting have reported 11% of pupils took regular prescribed medicine, although no further detail about their health status was reported (Mukattash et al., 2012) and Cherrill et al (2010) reported 23% children took regular medication, with 20% classed as having a chronic condition. Findings from PRESCRIBE suggest that health status and experience of the hospital setting are influential factors but it is difficult to capture detail about episodes with self-reporting.

5.6 Limitations of the study

5.6.1 Method

Utilising the format of a questionnaire did limit the opportunity for the researcher to clarify meaning and question participants further. Participants were instructed to seek help or advice if they did not understand but there were some discrepancies, for example; people who reported they took medication but did not disclose a medical condition. Focus groups would have been beneficial in allowing in depth discussion, however our PPI participants advised that CYP in school setting might find it intimidating having open discussions with classmates. Furthermore, they advised that questionnaires would allow people to make confidential disclosures regarding their health and medications which might not otherwise be reported. The difficulty was making sense of these revelations. In future research, clarification from parents could be justified to ensure illness and injury are classified appropriately. Alternatively gathering more information from CYP to allow a clearer picture of their health status would be beneficial, although there is the possibility that participants may then have questionnaire fatigue.

5.6.2 Time

Time constraints meant that the sessions lasted between 35-55 minutes, as sessions had to fit with school timetabling. All sessions were conducted in the same manner and same format however the available time did mean there were constraints on the level of discussion possible which could have led to differences in responses. Unfortunately, because the questionnaires were anonymised and entered manually after the session it was not possible to examine whether this was a factor in shaping perception. The sessions that were held at University enrichment days had attendees who were aged up to 21 years of

age. Their responses were discounted but it is possible that they influenced the discussion prior to questionnaire completion and may have influenced younger fellow attendees.

5.6.3 Comprehension

Preparatory information was provided to the participants about the process of research, the nature of PK research and the nature of hospital experiences however it was not possible to prepare them through visualisation of areas such as PIC. They were able to comprehend that when seriously ill they could be asked about participation in a trial however within group discussions they struggled to understand that illness or medical treatment might render them unconscious and therefore unable to join in the consent process.

5.7 How does this work with lay CYP address the knowledge gap surrounding pharmacokinetics?

Very few health research studies have been conducted within the context of the educational setting with a lay paediatric population. This is the first study the researcher is aware of to engage with CYP from a number of schools to identify their attitudes towards PK research. The study provides evidence that CYP are willing to consider participation in research and are motivated by the idea of helping others, as well as to improve their own health in line with other published literature undertaken with CYP (Cherrill et al., 2007, Cherrill et al., 2010, Mukattash et al., 2012). This is most apparent in year 12 and 13 students and amongst those of any age who had experienced a hospital admission. Although altruism appears to increase as CYP progress through school, so does concern about the recruitment of infants and young children. Factors that appear to facilitate participation are the provision of clear information and being involved in the decision-making process, although as this work was conducted using a hypothetical situation caution about over interpretation

is advised. Understanding more about lay perspectives is vital if a trial is to benefit future patients or the wider public (Piko and Bak, 2006). This work makes an important contribution to understanding more about the perspective of CYP who are current, or potential future service users.

5.8 Conclusion

Lay concepts of health and illness give additional important information to health professionals (Lawton, 2003). Very few studies have been conducted to explore 'healthy' CYP perceptions of research and none have specifically reviewed the topic of PK trials. CYP in this study were supportive of the idea of PK research and would consider personal participation, despite concerns about pain and decision making. As children age they appear to become more altruistic but also become increasingly concerned about the inclusion of those they viewed as 'vulnerable'. Those who had experience of the hospital setting appeared to be more likely to want to help others but researchers must take care in the design of future research to ensure material provides sufficient, clear information to CYP and that they are directly involved in decision making. Addressing pain, information needs and involvement in decision making are likely to be the most effective ways of improving receptivity to PK research. Although only 19% of this lay population included in this work would decline immediately, there was a high level of uncertainty, possibly reflective of a lack of education about research and an understanding of what is involved. This study found there was an enthusiasm for debate and to learn about hospital care and research amongst school age CYP. There is a possibility that through educating and informing an openness to research can be cultivated which will influence future public support for research.

Chapter 6: Exploring children, young people and parents' perspectives on Pharmacokinetic research in critically ill children

6.1 Background

6.1.1 Paediatric research

The strategy 'nothing about me, without me' emphasises the importance of decision-making in partnership with patients and families about health care (NHS England, 2017). This extends to decision making about research participation (Department of Health, 2003). There is a growing recognition that children may be able to express their own opinions about participation if these are sought, using appropriate methods to elicit them (Hart and Chesson, 1998). Despite this very little research exploring children's perspectives of health research has been conducted (Cherrill et al., 2007, Woodgate and Edwards, 2010). With increased understanding of their perspectives, their concerns and their motivations researchers can work to design studies which are acceptable to CYP and parents.

6.1.2 What is known about CYP attitudes towards pharmacokinetic research?

In a systematic review of the factors that motivate and discourage CYP and parents to participate in pharmacological research, less than half of the studies had considered the perspective of CYP than parents (16 compared to 37) (Tromp et al., 2016). There were also concerns that several populations were under-represented, including the views of healthy children, children with chronic diseases and critically ill children. When the field of pharmacokinetic (PK) studies specifically is considered, there were only three studies identified. Whilst Berg et al (2010) reported high levels of support for PK studies, only four

of the participants were actually CYP. The rest (n=46) were adult participants or parents. Errington et al (2016) had a higher participation rate with 23/ 100 participants being CYP. However Berg et al (2010) and Errington et al (2016) conducted the work by survey which limited the opportunities for further exploration of views. Only one study involved CYP being interviewed directly (by telephone) (Fogas et al., 2001). 91% of Participants within this study were supportive of PK research and would participate in a further PK study if asked. However, this may not represent the experience of all PK studies, as this study involved a single additional venepuncture and was conducted in an outpatient setting, with no requirement for additional visits or admission to hospital. Overall there is a lack of research exploring the perspective of CYP surrounding participation in PK research and no research addresses the question of conduct within an emergency or time sensitive situation. Future research must focus on the factors that shape the decision of children themselves (Tromp et al., 2016) and how these perspectives change in the context of hospital admission and in the face of critical illness.

6.1.3 What is known about parents' attitudes towards pharmacokinetic research?

Research surrounding parents' consent to participate in research has often focused on their understanding of randomisation and the consent process (Snowdon, 1997, Tait et al., 2002, Kodish et al., 2004). Whilst such research is relevant it cannot tell us what parents consider important about how information about clinical trials is communicated and their perspective of the recruitment process (Shilling et al., 2011). The systematic review conducted by Tromp and colleagues (2016) found the biggest factors for parents to consider participation in drug research was benefit for the child, altruism, a general trust in the safety of research and a

relationship with researchers. Discouraging factors were a fear of potential risks, a general distrust in research (their child as a 'guinea pig'), logistical aspects of the study and the disruption to daily life. Studies reviewing PK trials have focused on the attitudes of parents within the oncology speciality (Berg et al., 2010). However, these trials often take place in the context of phase I/ II trials and it is unclear the degree to which access to novel treatments influences decision-making. No studies have been conducted with parents within the PIC population and the influence of context and acute health deterioration on decision making has not been well-described. There are therefore large gaps in the knowledge base surrounding the perspective of CYP and parents, the factors that facilitate recruitment and also the influence of context on decision-making (see *Figure 22*).

Figure 22: gaps in the knowledge- CYP and parents' perspective

6.2 Research aims

As outlined in Chapter 2 the aim of this work was to determine the attitudes of participants towards paediatric PK studies, identify what participants perceived to be a barrier or problematic about the conduct of paediatric PK research studies and identify what participants' identify as enabling or facilitating the conduct of PK research studies. Please see Chapter 2 for full details of the methods undertaken.

6.3 Results

6.3.1 Demographics

Screening and recruitment took place from July 2013- July 2014. *Table 25* below includes details on where CYP were recruited from, their reported experiences and location of the interview / focus group. *Table 26* summarises the key information of age, gender and experience

Table 25: recruited CYP demographics

Participant	Age (yrs)	School Yr	Gender	Screened by	Recruited	Reported experience	Current medication	Experience[1]	Method	Location
56A	11	7	M	PIC	PIC	Nystagmus operation/ Sibling child on PIC	No	3	Joint Interview (56B)	Home
56B[2]	15	10	M	PIC	PIC	Patient on PICU	Yes	3	Joint interview (56A)	Home
70A[2]	10	6	F	WTCRF	WTCRF	Rare disease	Yes	3	FG 1	WTCRF
70B[2]	12	8	F	WTCRF	WTCRF	Rare disease	Yes	3	FG 1	WTCRF
70C[2]	10	6	M	WTCRF	WTCRF	Rare disease	Yes	3	FG 1	WTCRF
70D[2]	12	8	M	WTCRF	WTCRF	Rare disease	Yes	3	FG 1	WTCRF
75A	10	6	M	WTCRF	WTCRF	Fractured finger / sibling child in trial	No	2	Joint interview (75B)	Home
75B[2]	7	3	M	WTCRF	WTCRF	Cerebral Palsy	Yes	3	Joint interview (75A)	Home
81A[2]	15	10	M	WTCRF	WTCRF	Diabetes	Yes	2	Joint interview (81B)	Home
81B[2]	17	13	M	WTCRF	WTCRF	Diabetes	Yes	2	Joint interview (81A)	Home
82A	14	9	F	PPI lead	YPAG	Nil reported	Not asked	0	FG 2	WTCRF
82B	17	13	M	PPI lead	YPAG	Asthma	Yes	3	FG 2	WTCRF
82C	17	13	F	PPI lead	YPAG	Minor op	Not asked	0	FG 2	WTCRF
82D	15	11	F	PPI lead	YPAG	'Ill' as a child	Not asked	2	FG 2	WTCRF

Participant	Age (yrs)	School Yr	Gender	Screened by	Recruited	Reported experience	Current medication	Experience[1]	Method	Location
82E	15	11	F	PPI lead	YPAG	Skin allergies	Not asked	3	FG 2	WTCRF
82F	13	8	M	PPI lead	YPAG	Bone marrow donor	Not asked	0	FG 2	WTCRF
82G	12	8	F	PPI lead	YPAG	Asthma	Not asked	2	FG 2	WTCRF
82H	17	12/13	F	PPI lead	YPAG	Asthma	Not asked	2	FG 2	WTCRF
82I	17	12/13	M	PPI lead	YPAG	Cardiology	Not asked	3	FG 2	WTCRF
101A	12	8	M	Burns team	Burns	Burns HDU	No	3	Joint interview (101B)	BCH
101B	11	7	M	Burns team	Burns	Burns HDU	No	3	Joint interview (101A)	BCH
104[2]	10	6	F	PIC	PICU	Renal /PICU	Yes	3	Interview	Home
117A	17	13	F	Patient Experience Lead (PIL)	YPAG	Nil reported	No	2	FG 3	BCH
117B	15	11	F	PIL	YPAG	Chronic renal	Yes	2	FG 3	BCH
117C	14	9	F	PIL	YPAG	Nil reported	No	0	FG 3	BCH
117D	12	8	F	PIL	YPAG	Nil reported	No	2	FG 3	BCH
Total	26 participants									

[1]Experience: 0= No experience, 1= visitor to hospital setting, 2= experience of outpatients / ED, 3= experience as an inpatient [2]Has been / currently in a research study (n=9/ 26)

Table 26: summary of recruited CYP demographics

Demographic	Participants
Age	Range 7-17 years (median 13.5). Child aged 7 years old specifically wanted to take part)
Gender	13 Males, 13 females= 26 participants
Medication use	7: No, 11: Yes. 8: did not disclose
Hospital experience	None (4), visitor only (0), outpatient / Emergency Department (ED) visit (9), Inpatient (13); PIC admission (3)
Research experience	9: patients currently in / has been in a research study at some point

PIC: screening records were maintained by JCM and PIC research team. Records for a 7month period (September 2013- April 2014) reflect 850 PIC admissions (see left hand side of *Figure 23*). 122 admissions were over the age of 8 years (14%). Of these 44(36%) were ineligible due to pre-existing learning difficulties or acquired difficulties due to their illness / injury (discussed with parents and clinical teams) or child protection issues which made consent difficult. 63 (52%) were missed due to rapid discharge before the study could be discussed. 15 (12%) were provided with the Participant Information Sheet (PIS), 11 of which were happy to consider participation but did not respond to follow up. As a result, only one person was consented through this process. The other 2 participants with PIC experience (one former patient, one sibling) were identified through the PIC Family Liaison team. **WTCRF:** research participants were screened and recruited from WTCRF by JCM, following liaison with WTCRF staff. 15 CYP were screened, of which 11 were provided with a PIS. Ultimately six consented to participate with the study (all in clinical trials) (see right hand side of *Figure 23)*.

Figure 23: screening records for CYP admitted to PIC and attendees at Research Facility (WTCRF)

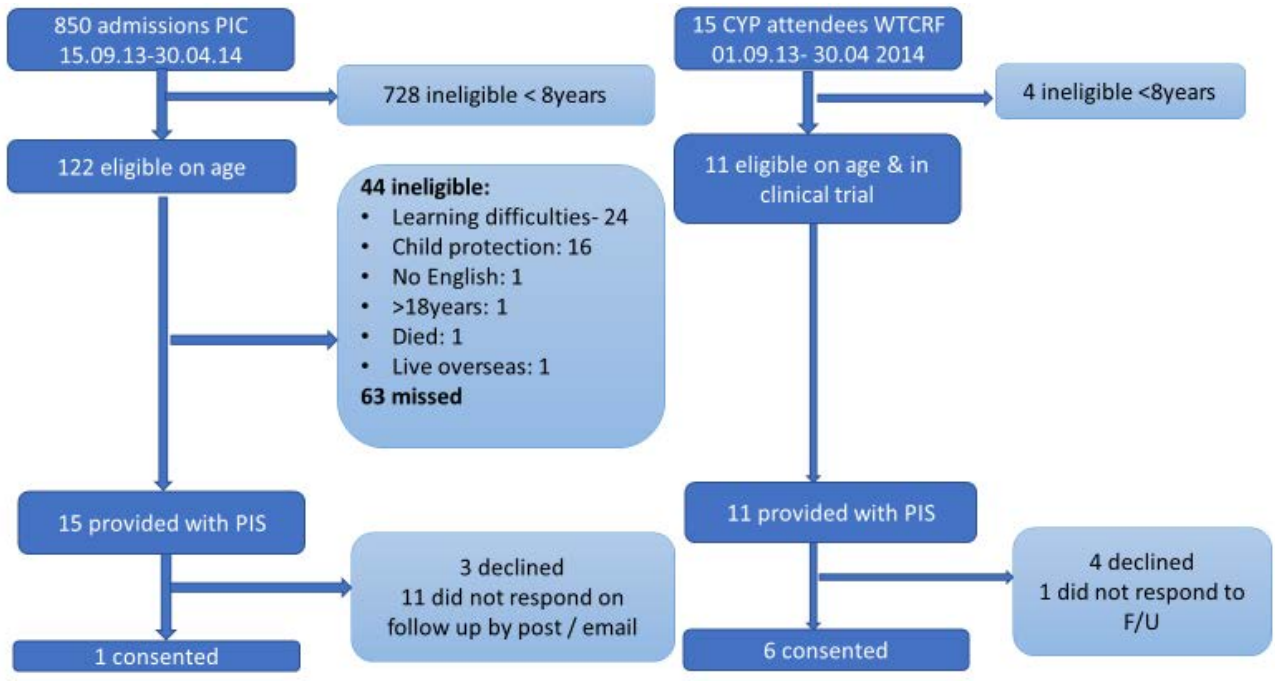


Table 27 provides details of parent/ carer participants, with summarised details of their research and health care experience in *Table 28*.

Table 27: recruited parent participant demographics

Participant	Gender	Child's age (currently)[1]	Level of experience	PIC/ NIC experience	Research experience[3]	Recruited from	Screened by	Interview location
71	F	10& 12	3	Yes	Yes	WTCRF	WTCRF	WTCRF
85	F	6	3	Yes	Yes	PIC / Cardiac	Family liaison	Home
86	F	6	3	Yes	No	PIC / Cardiac	PIC team	BCH
87	M	0.5	3	Yes	No	NIC/ Surgical day case	PIC team	Home
89	F	1.5	3	No	No	Respiratory	Specialist nurse	Home
92	F	6	3	Yes	No	PIC/ Cardiac	PIC	Home
102	M	10	3	Yes	No	PIC/ Burns	Specialist nurse	WTCRF
105A[2]	F	10	3	Yes	Yes	PIC/ Renal	PIC	Home
105B[2]	M	10	3	Yes	Yes	PIC/ Renal	PIC	Home
107	M	10	3	Yes	No	PIC/ Renal	PIC	Home
108	F	5&1.5	2	No	No	Surgical day case/ A&E	Family liaison	WTCRF
109	F	4	3	Yes	Yes	PIC	PIC	WTCRF
111	F	7	3	No	Yes	WTCRF	WTCRF	WTCRF
113	F	16 & 14	3	Yes	No	PIC/ Cardiac	Family liaison	WTCRF
114	F	4	3	Yes	Yes	PIC	Family liaison	Home
115	F	7	3	No	Yes	WTCRF	WTCRF	WTCRF
121	M	4	3	Yes	Yes	PIC/ Cardiac	PIC	WTCRF
122	F	7	3	Yes	Yes	PIC/ Cardiac	PIC	WTCRF

[1]Child's current age. For many their first point of contact with BCH was when the child was a new-born so they had been service users for a number of years.

[2] Married couple- interviewed together [3]Level of experience- 2= experience of outpatients / ED, 3= experience as an inpatient

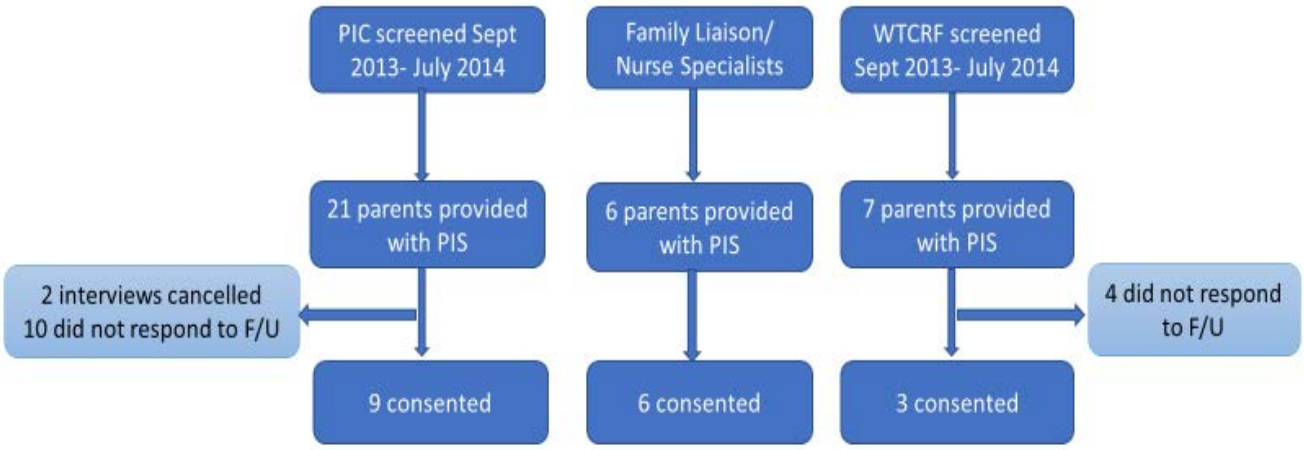
Table 28: summary of parent participant demographics

Participants	18- Mothers (13) Fathers (5)
Hospital experience	17 participants had experienced an inpatient stay in hospital with their child. 12 PIC/ HDU / NIC admission with their child (2 at other sites) 1 ED/ outpatient visits
Research experience	Participated in a research study (10) WTCRF (3) (rare diseases with PK sampling) PIC (6): 4 (observational studies), 1 (genetic study with blood sampling) 1(RCT with blood samples) Neonatal care setting (1) (genetic study with blood sampling)

Recruited parents / carers varied in the age of their child at the time of the interview (0.5-16 years) and their child's diagnosis (although there was a high proportion of parents of children with congenital heart disease, reflecting that 50% of PIC admissions are for heart surgery). 17/18 (94%) had experience of an inpatient admission to hospital with their child, compared with 13/26 (50%) of CYP.

With limited resources, the focus was placed on screening for CYP as this was recognised as being the more challenging group to recruit to. The PIC Research team screened for families where it was appropriate to consider a home visit on grounds of distance, child's prognosis and lone working for the researcher. See *Figure 24* below for a summary of recruitment.

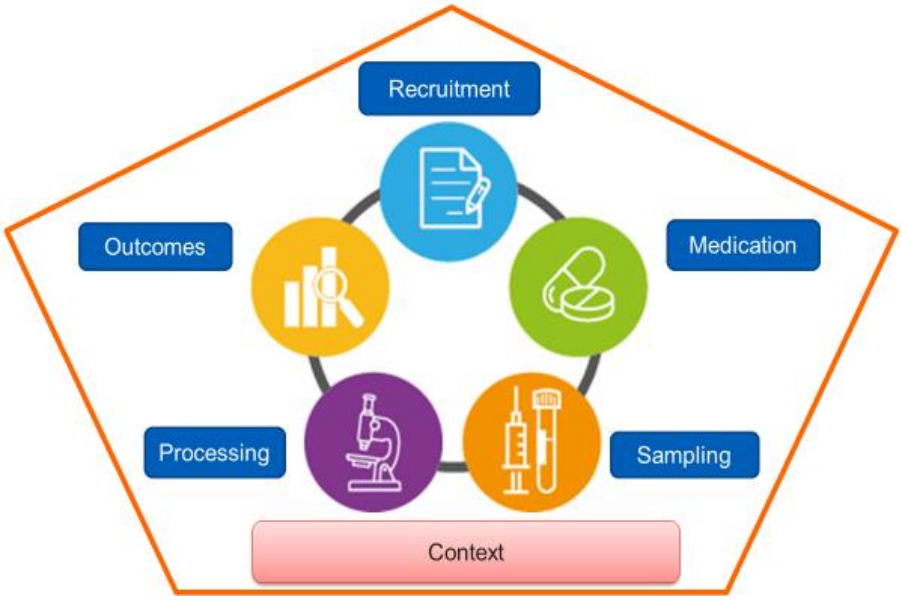
Figure 24: screening and recruitment records for parents (2013-2014)



6.3.2 Themes

There were six key themes identified within participants' responses, reflecting the journey of the patient and their family through the research process see *Figure 25* below. Running throughout these was the influence of context at the local level, the wider organisational level and beyond. This reflected aspects identified within the I-PARIHS model (Harvey and Kitson, 2016).

Figure 25: thematic analysis results: core themes



Attitudes towards PK research are highlighted first. Then within each theme problems or barriers to conducting PK research and factors which enabled or facilitated conduct were identified. Barriers are discussed first with facilitators summarised at the end of each theme. As facilitators could address a number of barriers there was some cross-referencing. Quotes from CYP are cited as CYP- then individual study number. If this was conducted as part of a FG there is an additional letter to differentiate participants. Parents are cited as P- individual study number.

6.3.3 Attitudes towards PK research

6.3.3.1 Parents'/ carers' attitudes

Parents and carers attitudes reflected the influence of multiple factors during their assessment of the risks and benefits of participation (see *Table 29* below).

Table 29: summary of influential factors on parents' attitudes towards PK research

Positive comments (50%)	Negative comments (50%)
• Nature of the disease • Experience/expertise (chronic illness) • Group affinity • Act in best interests of child	• Vulnerability /fear • Health status • 'Experimentation' • Study requirement • Child with communication/ comprehension difficulties

Positivity towards PK research was particularly evident from families with experience of a child with a rare disease, in situations where there were few treatment choices and best interests were therefore felt to be clearer or where families felt an affinity to a community of children with a chronic disease:

> *"I think in our case we would because we would already have had the background of knowing that they'd got a rare condition that there wasn't a treatment for, so we would already have had the mindset of promoting research really." (P-71)*

Concerns about PK research tended to focus on the requirements of a protocol and the impact of this for the individual CYP. This was of particular concern when the CYP was acutely unwell:

> *"...however pro-research you are, it becomes difficult when it is your own child, which is terrible to say; that's **my** baby... I think it is a big issue." (P-86)*

It was also an issue for families of a child with communication or comprehension difficulties. There were comments from such families that preparing for and managing routine investigations / health monitoring was already challenging, without additional burdens from research:

> *"My son is not going to tolerate anything- he's autistic, he's very stuck in his ways. He doesn't communicate or talk... he hates anything new… he won't sit still*

for long, he gets distressed, he gets sick... and he doesn't like pain, he doesn't like anything with needles..." (P-107)

Some parents reported that there was stress about the uncertainty research raised; both from decision-making about whether to participate, but also from the realisation that Doctors did not have all the answers to managing their child's condition

"I understand that my daughter wouldn't be here if it wasn't for people in the past that have progressed, so that's where you're caught. Totally, you have to do this. You have to it, but I'm just saying as a parent, it is ***extra stress.*** *It's extra stress because you don't know if you're doing the right thing" (P-121)*

Overall parents' attitudes reflected a risk: benefits assessment about participation of their child in PK research. Most were willing to consider participation (see *6.3.8.2.3*)

6.3.3.2 Children's attitudes

CYP were less focused on risk: benefit analysis about PK research than parents and instead focused on aspects influencing their decision-making (see section *6.3.4.1* below). CYP appeared to think more positively about PK research with increasing age, with increased experience of health care and when they had expertise in the management of chronic health conditions. There were also comments about the positive attitude towards research held by those with chronic health conditions or who felt affiliated to a 'group' (See *Table 30* below).

Table 30: summary of CYP attitudes towards PK research

Positive comments (58%)	Negative comments (42%)
• Age • Experience/ expertise • Identify with a group	• Vulnerability / fear • Age • Health status

Negative comments reflected that being older and more experienced did not necessarily equate to increased receptivity to research, particularly in the context of being acutely unwell. Understanding and comprehension about PK research could be challenging for CYP, particularly the rationale for additional unpleasant procedures.

Overall CYP appeared to be supportive of PK research, particularly amongst those who feel they have benefited from other's participating in research and were willing to consider participation in a PK study (see section *6.3.8.2.3*).

6.3.4 Recruitment

The recruitment process was by far the most discussed aspect of PK research conduct amongst CYP and parents. Within this sub-theme many discussions focused on factors influencing the decision-making process.

6.3.4.1 Decision-making about participation in PK research

Overall there was a high level of congruence between CYP and parents, with 5 / 6 sub-themes the same (see *Figure 26* below). Where the groups differed was the focus of parents on the influence of novel treatments, the value of personal benefit and the emphasis CYP placed on joint decision-making.

1. Helping others

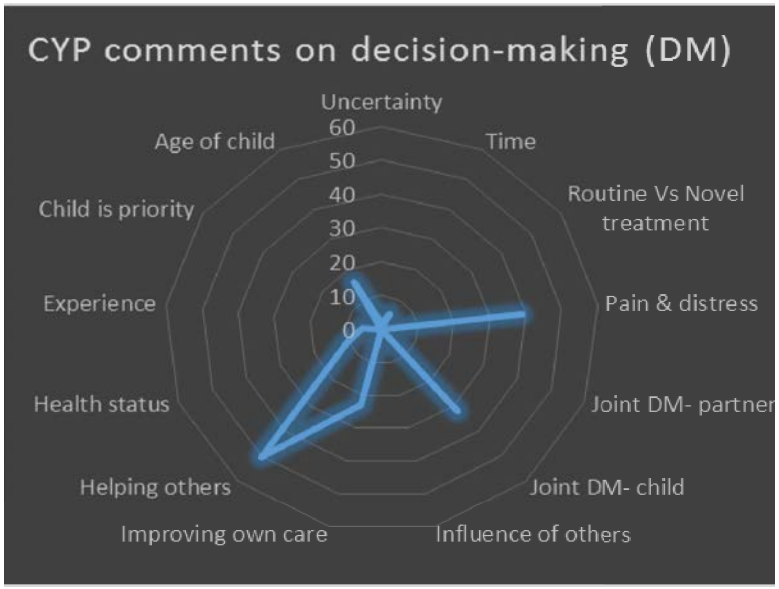
Overall both sets of participants were supportive of the idea of taking part in research which would help improve care for others in the future:

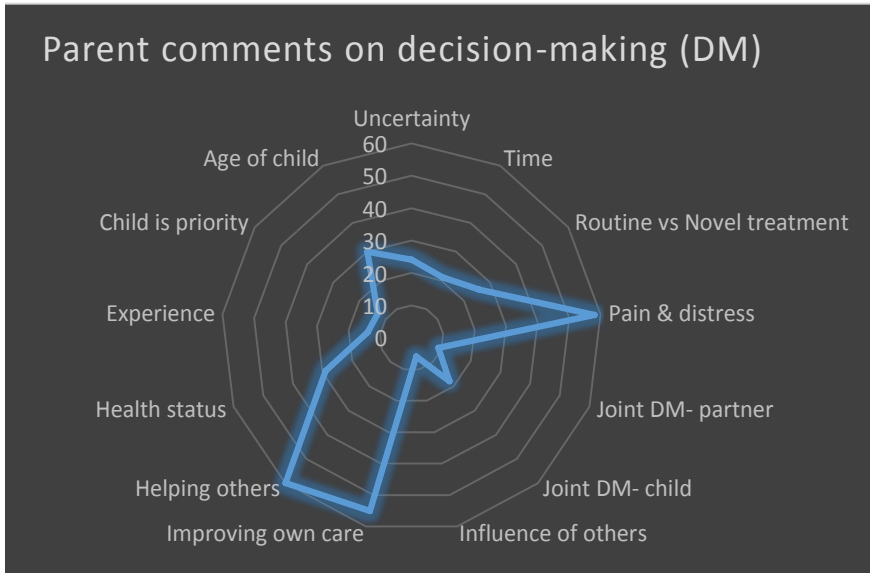
> *"Because I'd want to think that people are getting the same support as me or even better support, being able to get the right medicines and all that because it's not fair when children are ill, especially at such a young age" (C-104)*

Some accepted that involvement might not bring any personal benefit, but this was acceptable as long as there was none - minimal pain or inconvenience to the CYP. Others would consider participation, even when this involved extra blood samples:

> *"All these samples... all these studies eventually join up into a bigger picture... and that's how you've got to sell it... "yes, your blood sample, it's not going to change the world, but it's going a long way towards it, without yours it's one less." (P-107)*

Figure 26: number &distribution of comments made by CYP & parents about decision-making (DM)





The degree of altruism therefore varied and where participants made negative comments, these tended to reflect inconvenience or discomfort to the child:

> *"I know people do want to try and help in those situations but I mean when you're in that specific situation. You're not really thinking about other children, you're just trying to focus on your own child" (C-82H)*

2. Pain and distress

For both CYP and parents the idea of pain and distress was hugely influential when considering participation. Both CYP and parents highlighted the stress and upset having a cannula sited or having a blood test taken could bring:

> *"I would never, I **don't do** blood tests unless they're absolutely necessary. I won't take part in any trial or anything like that. I'd love to you know, have the confidence to do it but I've got a fear of needles and I can't take an injection or you know, or do a blood test, I can't do it..." (C-82B).*
>
> *"Yes, he gets very distressed with having cannulas put in and I mean every visit that we have to the hospital, he always says, "Mummy, have I got to have a cannula?" Even for a check-up" (P-92)*

If the study involved additional painful procedures which were not clinically indicated many felt this was too much and stated this would influence them to say no. However, if the child was sedated and had good pain management or already had lines in place for sampling then additional sampling was regarded as more acceptable:

> *"And if he was on morphine or something, or strong drugs, then he wouldn't really have been too aware of it happening and I would say yes, they could put another cannula in to take the bloods." (P-92)*

3. Personal benefit

There were a large number of comments from 13 parents about the motivating influence to participate in PK research if there was personal benefit for their child. Most viewed this participation as an enhanced form of care or an extra level of reassurance:

> *"We want to make sure he has the best antibiotics or the best pain relief possible and if to achieve that... we have to measure blood levels, fine. It's making sure that he gets the **absolute best.**" (P-102)*

10 CYP acknowledged that they would be motivated to take part in research to benefit their own care, of which six were in a clinical trial at the time of the interview. However overall there were fewer comments from CYP reflecting the personal benefits of participation, suggesting that personal benefit was not the most motivating factor for them.

4. Age of the child

Both CYP and parents commented on the influence of age on decision-making about whether to participate or not. Despite concerns about the involvement of infants, there was recognition from participants (both groups) that conducting PK research with infants could

be 'easier' as they had less anticipatory anxiety, less understanding of what was taking place and also would not remember procedures such as blood sampling:

> *"If anything, babies are the easier ones to do the study on… because the older ones have more objections. "(P-109)*

Participants were not specifically asked at what age they felt CYP could join in with decision-making process, but many did suggest or debate ages. Suggestions from CYP ranged from 6-11 years and parents ranged from age 5 - 16 years of age, although there was widespread recognition that this would vary according to the individuals concerned. Age could serve as a guide but ultimately much would depend on the individual child and family:

> *"I could have signed up for either of my children but I know they would have responded differently and so for one child, I could see that I would have gone through with it but for another, it would have been more difficult to stick with that" (P-86)*

5. Involve CYP

The main area the two groups differed on was the relative prioritisation of joint decision-making with the CYP; this was the 3rd most commented on aspect for CYP and the 9th for parents. 21 CYP (81%) made reference to the fact that CYP should be involved in decision making about participation in research and should be asked directly wherever possible:

> *"If they were asleep or ill, I'd probably like wait until they were like better or woken up so then they could... know what they were going to be going through. You need to get their opinion, instead of the parents' opinions because you don't know if they want to do it or not" (C-75A)*

6. Health Status

A number of comments reflected the influence of the child's health status at the time of being eligible for research. Parents' concerns tended to focus on the invasiveness or relevance of the study to the CYP current condition. CYP focused in on more specific aspects of health and wellbeing such as feeling ill, feeling tired and the influence of medications on an ability to make decisions:

"Not really because you are not in the best state of mind, kind of, you just want some privacy and to be left alone." (C-56B)

These were the main themes influencing CYP. For parents, other influences such as 'novel treatments', uncertainty, time, experience, the prioritisation of the child were identified, however these were in smaller numbers.

6.3.4.2 Barriers to recruitment

Overall the biggest barriers to decision-making about PK study participation from CYP and parents' perspective were pain and distress, the age of the child and their health status at the time of approach. In addition, other barriers / issues were identified during discussions surrounding recruitment (see *Table 31* below for a summary of barriers and facilitators).

Table 31: summary of barriers and facilitators to recruitment (CYP and parents)

	Barriers	Facilitators
Recruitment	'Vulnerable' individuals	• Having a choice • Personal benefit • Helping others • Levels made available for care[1] • No additional samples / sampling procedures
	Severity of health status	Deferred consent[1]
	Pain / distress	• Analgesia • Use of indwelling lines for sampling[2]
	Age: both younger and older	• Appropriate communication • Personal benefit • Involve CYP
	Communication/ comprehension difficulties	• Preparation • Communication • 'The approach' • Support joint decision-making
	Extra appointments Missing school Missing work Travel and parking	Reduce impact for individuals ○ 'Piggy backed' appointments ○ Flexibility ○ Home visits

[1] Discussed in *6.3.4.3.9*, [2] Discussed in *6.3.6.2*

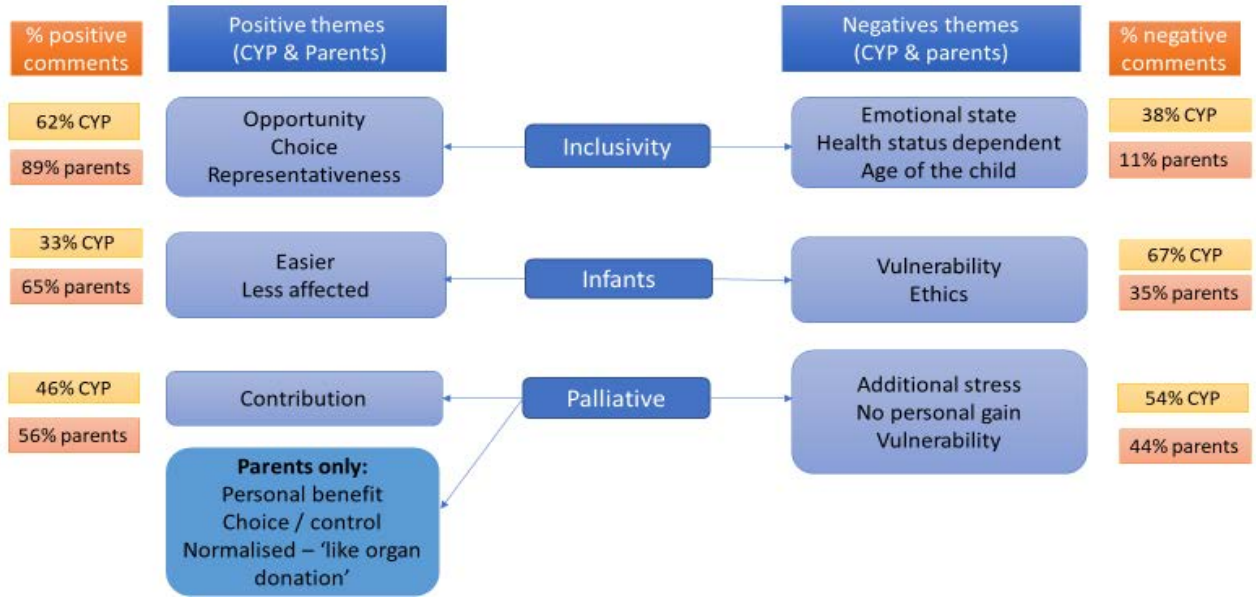
6.3.4.2.1 Vulnerable study participants

Both CYP and parents were mostly positive (62% of CYP, 89% of parents) about being inclusive about who was approached to participate in PK research, recognising the need to include different types of people in PK research:

"...the way I look at it is the disease or whatever, that's not going to choose which age group to affect, so you're going to have to test the medication in all ages." (P-105B)

However, there were concerns about patients they felt were 'vulnerable'; in particular infants (CYP) and those on palliative care pathways (CYP and parents). These 3 sub-themes are identified in *Figure 27*. Positively themed comments about their inclusion are summarised on the left and negatively-themed comments to the right.

Figure 27: summary CYP & Parents attitudes towards PK study participants



Concerns about infants reflected their perceived vulnerability, their limited communication capabilities and the ethical difficulties associated with being unable to involve them in decision-making:

"It's hard to ask for a baby (agreement from all). It is all right if they're older and you can ask them as well as their parents but obviously, the babies, you can't. And then you don't understand the pain that they're going through because they can't speak." (C-117D)

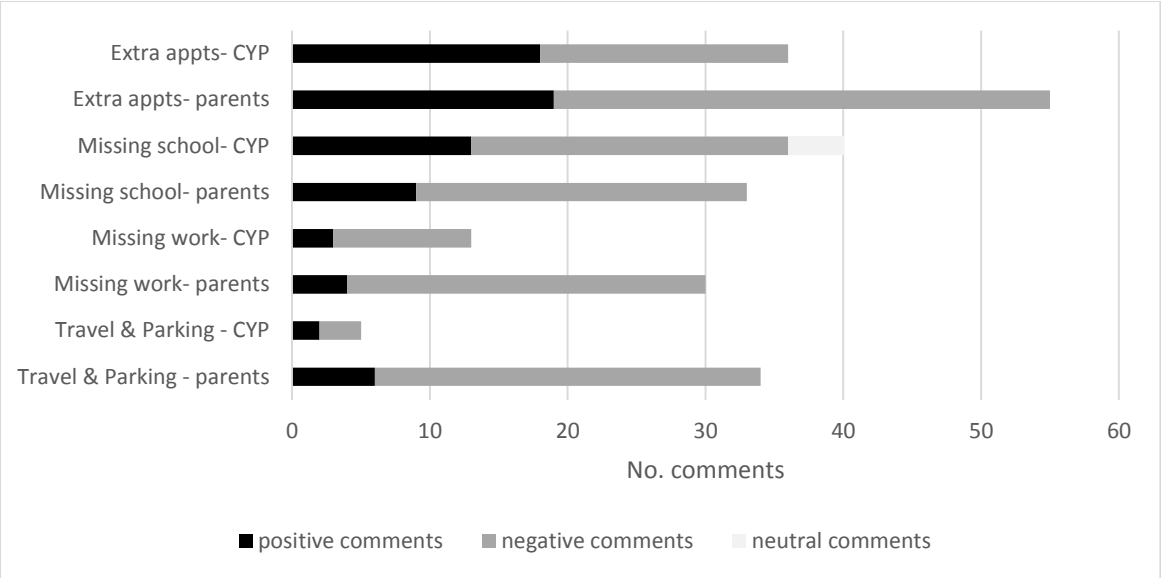
There were also some concerns about inviting patients on a palliative pathway to participate because of a lack of personal benefit and a concern about adding burden or distress:

"I would say if you know the wee child is not going to make it the last thing that parents need is to think of their kid as a lab guinea pig... respect the child" (P-121)

6.3.4.2.2 Hospital appointments

The subject of hospital appointments specifically for research yielded a high number of comments from CYP and parents which were felt to influence decision-making (*Figure 28).*

Figure 28: CYP and parents' attitudes towards research appointments



Overall extra appointments were viewed negatively by parents, particularly those whose children who already required multiple attendances at hospital. Responses ranged from classifying these as inconvenient to annoying, disruptive and time consuming:

> *"I think it'd be incredibly hard dealing with the whole **extra** hospital visits. It's hard enough being on a trial and having *'s other hospital appointments at <names another tertiary children's hospital>... It's draining. It's not just a five-minute appointment... Generally, it's a whole day, which is time consuming and quite hard." (P-115)*

Parents of children with chronic conditions recognised that a certain amount of school would be missed. However, there were thresholds of acceptability and extra visits posed a problem:

> *"...she's in year 6 and she starts secondary school in September, and she's lost a lot of school already so that would be a concern for me" (P-105B)*

Although CYP were less negatively opinionated than parents about the idea of extra visits, they became more concerned if attendance required them to miss school. There were 52 comments by 20 CYP identifying the importance of education, particularly for children who had to attend hospital regularly. The issue also increased in significance as pupils progressed through school, with CYP identifying the challenges of catching up on lessons missed:

> *"I used to love missing school for my appointments. I used to drag it on, ask pointless questions [laughter] but now, I try and get in and out because I can't catch up otherwise." (C-82B)*

Parents were also extremely concerned about missing work to attend hospital appointments with their child and there were accounts of parents stopping work due to the amount of appointments some families were required to attend. There were also comments about the need to prioritise appointments and although managers were sympathetic to parents' situations there was a finite limit to how much time could be taken off work:

> *"...if it was an essential appointment you get time off work but I don't think your managers will be happy if it is just for research purposes. Sorry!" (P-109)*

Parents were also extremely concerned about the travel and parking associated with attending a hospital appointment:

> *"For us it is a nightmare because we live in *. To drive it is an absolute bloody nightmare, quite honestly. You know all the way in, where am I going to park? Will I get a parking space? How much is this going to cost me? I've come here before and it costs me nearly £10 just to park the car for a few hours. That's a lot of money when it's regular" (P-113)*

Offering to reimburse parking or travel expenses to compensate for extra research requirements was felt by some to assist with this, however, for many the message was clearly that research alone would not be sufficient motivation to have to attend for more appointments.

6.3.4.2.3 Summary barriers to recruitment

In summary, there were many issues surrounding recruitment to PK research for CYP and parents. Decision-making was felt to be negatively influenced by the potential for pain and upset to the child and the requirement to make decisions at a time of deteriorating health status. Both groups were concerned about vulnerable populations, with CYP concerned most about the inclusion of infants and parents most concerned about palliative patients. Both groups felt additional hospital appointments were problematic, particularly missing school and parents also commented on the problems of missing work and the challenges of travel.

6.3.4.3 Facilitators surrounding recruitment

Facilitators identified by CYP and parents are discussed below.

6.3.4.3.1 Having a choice

Despite concerns about the inclusion of infants and palliative patients deemed vulnerable, very few participants made generalisations about their exclusion from research. Many felt families valued having a choice and the opportunity to contribute to future health care as well as the potential for personal benefit, such as improved pain management. There were also comparisons to that of organ donation; recognising that conversations about donation, whilst extremely difficult, are now recognised as accepted practice. Over time, being approached about research could also be normalised and become more acceptable:

> *"...like when you do organ donors… there are questions that are going to be asked. Their child's too poorly and they've done everything they can so you have to ask about organs, don't you? It is the same as asking about organs." (P-107)*

6.3.4.3.2 Emphasise the benefit of participation (personal /for others)

CYP and parents highlighted the importance of offering some form of personal benefit or enhanced level of care for the child from participation:

"I think people are more likely to agree to taking part in the studies if they see a benefit to them... an extra review afterwards... and review the bloods... I don't know why anybody would say no to that." (P-114)

This seemed to be a particular priority for parents. Both CYP and parents were also highly motivated by altruism. If a study could outline the impact of research for other CYP and families many participants felt this was a motivational factor, even for young CYP:

"I think all children understand the concept of helping other people... If we said this is going to make you a little bit uncomfortable now but it will help lots of other children, I think even from a young age they could understand that..." (P-71)

6.3.4.3.3 Communication and 'the approach'

Communication is fundamental for all aspects of care, but parents specifically highlighted the importance of getting the level and depth of communication about research right to aid decision making about participation. This took the form of both verbal and written communication in simple and easy to understand formats:

"You give them the leaflet, this is what you're signing up for, parents know if they can commit to 18 hours of sitting around in hospitals, or they can't" (P-107)

There was also specific reference to the importance of the initial contact with families about a PK research study. These highlighted that it was not just what was said but also the timing and sensitively of the approach:

"Yes. I think it is in the manner it's done and the timing. That's the big thing, when is the right time to approach the parents and ask them really? I think once you've got that balance, you're more likely to get parents' consent." (P-108)

Crucial factors related to the personal skills of the researcher and their ability to interpret the situation. Key elements are listed in *Table 32* below.

Table 32: 'the approach': influential personal skills and situational factors

'The Approach'	
Personal skills	**Situation**
Trustworthy	Timing
Courteous	ID badge
Personable	Clear role
Clear explanations	Relationship with clinical team
Tactful	Visible liaison with clinical team
Correct 'pitch'	
Receptive	
Sensitive	
Provision of appropriate information	

(from 16 parent participants)

6.3.4.3.4 Involvement of significant people

Recognising that CYP were extremely concerned about being excluded from decision-making about research, a key facilitating factor was to ensure that involvement of CYP was a priority for researchers:

> *"I'd be a bit annoyed... I know that you're only doing it for the best but I'd be like "Why are you taking things from me?" ... I know I'm in a state at the moment and like I could die... But then at the end of the day it's my personal information, you know?" (C-104)*

Parents also recognised the importance of facilitating the CYP's involvement to make shared decisions with them (although less so than the CYP themselves), but they also wanted to consider shared decision-making with spouses/partners. They highlighted that making decisions about research was challenging and the consent process needed to involve other people deemed important to the parent with parental responsibility.

6.3.4.3.5 Preparation

Parents felt that informing people as early as possible about the PK research taking place would help to prepare and support them with decision-making. This extended to preparing families prior to their admission, particularly for those having elective surgery:

> *"...if his operation was in 3 months' time, and this information came through in the envelope with the appointment letter and it gave me the option to have a*

think about it, read about it and do some research into the research study, then yes, it is definitely something that would be helpful to me." (P-87)

Parents recognised that this information might not be thoroughly ingested if it was perceived not to be relevant, however it might help at least prepare families for being approached about a research study. Some parents also highlighted the value of other sources of information to help families make decisions, such as websites featuring accounts from other families:

"That would help me immensely because if I was willing to take part in the research. it would be good for me to go on to a website and just have a look at what other people's experiences are and it might help me make my decision that bit quicker." (P-87)

6.3.4.3.6 Analgesia and distraction techniques

Recognising the negative influence of anticipated pain, CYP and parents recommended the usage of topical analgesia to reduce pain. Provision for local analgesia should be incorporated within a study protocol to help address anxieties associated with procedural pain. Seven parents also made reference to the use of distraction and play therapy to help their child to cope with procedures required for routine hospital care:

"the play specialists were fantastic. Absolutely fantastic... They play a very important part, they really do. Because once we got over that, it was plain sailing." (P-113)

This suggests that play therapy and distraction techniques could play a role in facilitating patient and family engagement with research.

6.3.4.3.7 Reassurance about safety

Confidence in the safety of a study is fundamental for CYP and parents. Parents identified that if research and clinical teams had a good relationship and could be seen working together this was viewed positively:

"If the doctors on the round says we spoke and it seemed to be more of a team affair rather than just a lone person walking around doing things then that would be good." (P-109)

Seven CYP and thirteen parents reported that guidelines which referenced acceptable blood sampling volumes would provide reassurance that a trial was safe and therefore increase their likelihood of participation:

> *"...if they said well yes, these are the national standards or the agreed limits for taking blood from children and this is within that range, then that would give you a bit more confidence." (P-71)*

However, there was a recognition this should still be reviewed for each individual CYP, to ensure their individual situation was considered.

> *"…at the end of the day, they're only guidelines, they're not applied to every... individual person. It says there's a certain number of units of alcohol you can have before you drive, but I would **never** have any alcohol before I drive... So <reference to guidelines> wouldn't give me any confidence whatsoever" (C-82B).*

6.3.4.3.8 Avoid / combine research appointments

Extra hospital visits, travel and parking expenses, missing school and missing work were significant issues for CYP and particularly parents, even those strongly supportive of research. Facilitation measures therefore need to reduce the impact for the individual and their family. See *Figure 29* below for a summary of participants' views on different approaches. From these the top three preferences for each group were compiled after ranking the percentage of positive to negative comments. These are summarised in *Table 33*.

Figure 29: CYP (L) and parents' (R) perspectives on alternative approaches to research appointments

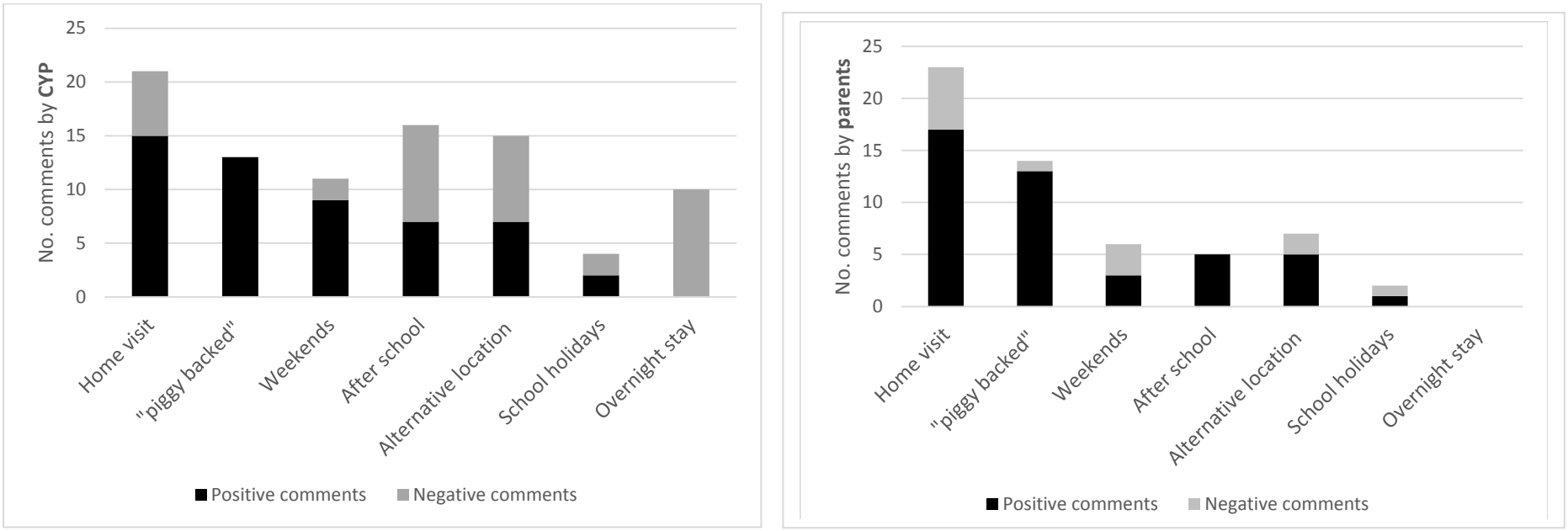


Table 33: top 3 preferences for research appointments (CYP & Parent)

CYP	Parents
1. Piggy backed to clinical care	1. After school
2. Weekends	2. Piggy backed to clinical care
3. Home visits	3. Home visits

1. 'Piggy backed' research

Overall the concept of adding research appointments to routine clinic appointments was viewed extremely positively. 100% CYP (n=13) and 90% parents (n=10) supported the approach:

> *"I think you could arrange it so it coincides with another appointment that you already have. So, you're not missing any more school, then that might be better" (C-117A).*

2. Flexibility with appointments

Weekend appointments were the second most positively viewed approach by CYP and after-school appointments the second most positively viewed by parents. Although the groups differed slightly in their preferences, the rationale for both was to avoid missing school, therefore, flexibility in appointments appeared to be the key message.

3. Home visits

Eight CYP and eleven parents were supportive of the idea of home visits from research staff, based on rationale that this was better for the individual and offered enhanced privacy. However, this was not universally popular, particularly from a safety perspective:

> *"I'd feel safer in the hospital because I know then you've got intensive care upstairs so you could just go there if anything happens. Whereas here, you've got to get the ambulance and if anything, is to go wrong, it could be life threatening…" (C-104)*

6.3.4.3.9 Consider different approaches to traditional PK approaches

In order to overcome some of the issues and concerns raised, alternative approaches from the PK literature were discussed. *Figure 30* below summarises both groups' attitudes towards a number of these, with *Table 34* summarising the top four approaches. Overall the groups rated the approaches very similarly and were relatively positive to all alternative methods.

Figure 30: alternative approaches to traditional PK studies (CYP and parent)

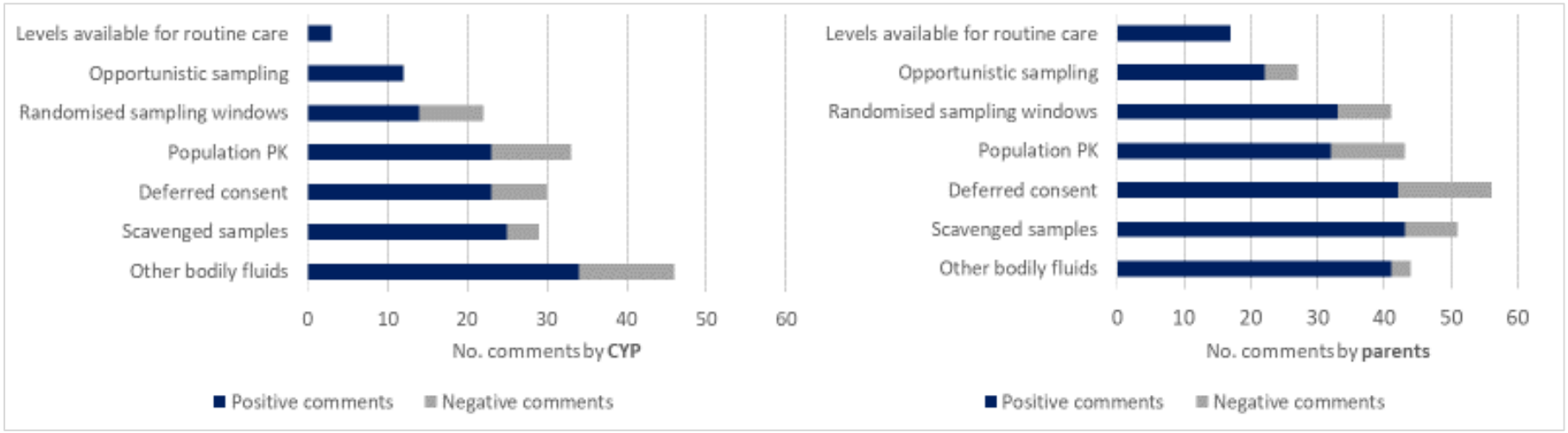


Table 34: summary: alternative approaches to PK studies (CYP & parent)

CYP	Parents
1. Opportunistic sampling / Levels available for routine care	1. Levels available for routine care
2. Scavenged samples	2. Other bodily fluids
3. Deferred consent	3. Scavenged samples
4. Other bodily fluids	4. Opportunistic sampling

1. 'Research' levels made available for clinical care

CYP and parents felt that if PK measurements were taken for research care, these should be made available for clinicians managing their clinical care, particularly if this was not normally available. Although there were not large numbers of comments about this approach, there were no negative comments about this approach:

> *"So, you just say look, this is the graph of the results we took... and it shows you... the pain he was in, this shows what drug he had and what happens as he came off... And it's kind of like, if the results are there available in their notes to use... to say this is the results we've got that helps." (P-102)*

2. Opportunistic sampling

Opportunistic sampling, or sampling alongside clinically indicated bloods, did not receive any negative feedback from CYP and overall was rated positively by 8 CYP and 9 parents:

> *"Yes, that would definitely be better because then you have less chance of infection. Because infection control is very important. * did actually get an infection from the line that he had put into him." (P-87)*

Negative comments reflected a concern that it must be clear what the samples were being taken for, as well as recognising that these were still in addition to clinically indicated bloods and therefore still had the potential to lead to anaemia.

3. Scavenged samples

Overall the use of 'leftover' samples rated highly amongst parents and CYP. Participants liked the idea of avoiding waste of samples which had already been taken for routine purposes:

> *"Yes, I think you should. I think if it is already out, you may as well use it for other things." (C-56B)*

Concerns related to why there was any excess blood to be able to measure levels from. Participants felt this could create some concerns and uncertainty for CYP and families:

> *"I think some parents might be a bit sceptical I guess, "Did you do that on purpose?"" (P-108)*

4. Other bodily fluids

The use of saliva or urine instead of blood was another popular alternative approach, with 74% of CYP comments and 93% of parents' comments positive to the idea. It was regarded as easier, less painful and a productive use of a waste product:

> *"I think I'd rather go to the toilet than have something stuck in me" (C-82A)*

Negative comments related to the difficulty of obtaining time specific samples, the issue of children who cannot void on demand, issues related to embarrassment as well as some of the practicalities associated with obtaining samples:

> *"But then some people don't know like weeing into a pot, 'cos I don't. It's hard. Particularly if you're a girl!" (C-104)*

5. Deferred consent

Within both CYP and parents there was some support for the idea of deferred consent. Those that spoke positively recognised that admission to PIC was an extremely stressful time and appreciated the fact this method would not delay treatment or require them to make a decision about research immediately:

> *"I think when your anxieties are very high and you are not sure what is happening, you are so out of control aren't you? All you can think about is your child and their safety and their health, so I think like you say, when it has calmed down it is a very different kettle of fish isn't it, because your anxieties pass, you can think more rationally." (P-85)*

CYP and parents who were unsure about this approach were those who felt strongly that they should be able to consent to everything being done to their child **before** it was done, rather than afterwards:

> *"I think for most parents the issue would be with taking it in the first place, not the using it." (P-71)*

Overall approaches which avoided additional blood sampling, made use of samples already taken or were perceived to offer an enhanced level of care were the most valued by CYP and parents.

6.3.4.3.10 Summary of facilitators

Appropriate communication, preparation and consideration of 'the approach' by research professionals have all been identified as positively enhancing the recruitment process. The optimum study design would offer some form of personal benefit to participation as well as a clear outline of how this will benefit other CYP in the future. Addressing these factors would help to mediate concerns about vulnerable populations. Ideally, additional painful procedures are avoided, taken alongside clinically indicated samples or utilise leftover samples. Alternatively, procedures are undertaken whilst receiving analgesia and the use of distraction and play therapy is recommended. Researchers need to facilitate the involvement of significant others in decision-making about research, including CYP. To reduce the burden of research, researchers need to minimise or avoid additional hospital appointments through 'piggy-backing' them to clinically indicated appointments or offering flexibility in their timing.

6.3.5 Medication

6.3.5.1 Barriers/ challenges with medicines

Taking a medication in a prescribed manner is a key aspect of a PK study. Despite only 11/ 26 of CYP reporting being on medications at the time of the interview, 18/26 (69%) CYP and 13/18 (72%) of parents identified issues surrounding the administration of medicines to children, (see *Table 35* below).

Table 35: summary of barriers and facilitators associated with medications (CYP & parents)

	Barriers	Facilitators
Medications	Administration Tablets Palatability Changing meds for research purposes	Check individual preferences

Problems related to being able to take medicines in the form dispensed, knowing what to do if the CYP vomited as well as difficulties obtaining prescriptions:

> *"when we went to the chemist, the pharmacy to get the renewal prescription, they wouldn't give it to us because the steroids were... the dosages were more than an adult would have. And they actually had to query it and had to double check it before they would give it to us." (P-113)*

Both groups recognised that taking tablets and the palatability of medicines were significant issues (see *Figure 31* below), with 80% of parents asked (12/15) highlighting concerns. Even parents of adolescents cited examples of their children struggling to take them:

> *"Get him to swallow something whole? No. No chance." (P-102. Parent of a 12-year-old)*

This was confirmed by adolescent participants themselves:

> *"...I physically can't swallow a big tablet. I just literally regurgitate. I'm not scared of taking tablets, I just can't swallow them. I'm such a baby" (C-117B, aged 15 years).*

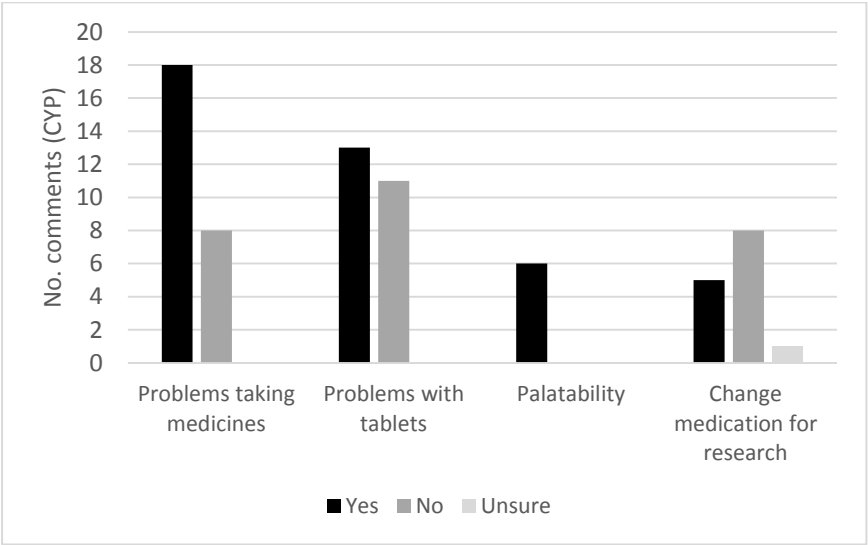
Where palatability was discussed (9/26 CYP and 10/18 parents) it was identified as a significant issue (67% of CYP and 80% of parents):

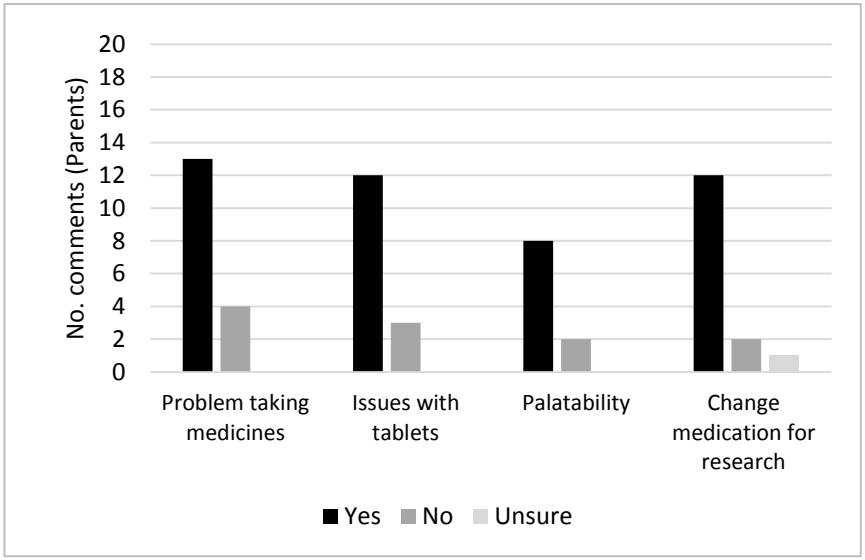
> *"It tasted like strawberries mixed in with poison" (C-75A discussing*
>
> *Benzylpenicillin)*

This would be an issue for participants in future PK studies, particularly if a study involved a new preparation which had not conducted consultation over taste, colour and smell. Despite issues identified with medications, there was some reluctance amongst participants to change medications for a research study:

> *"I think I'd want figures, to be honest. I think I'd be more protective from now on just because of what he's been through really. I don't like the idea of new drugs being tested. Old drugs with different doses, change in the dosage, I wouldn't be so alarmed about really. Definitely a new drug, I'd be a bit apprehensive." (P-122)*

Figure 31: experiences and attitudes towards medications (CYP & parent)





6.3.5.2 Facilitators associated with medications

The main facilitator identified from participants' responses was to engage with CYP and their families about medications before embarking on a research project. Studies need to address medications which actually pose an issue for CYP and also ensure that the proposed alternatives are available in appropriate, palatable formulations.

6.3.6 Sampling

Participants made many comments about issues surrounding sampling for PK studies. Barriers and facilitators are summarised in *Table 36* below.

Table 36: summary of barriers and facilitators related to sampling (CYP & parents)

	Barriers	Facilitators
Sampling	Capillary Cannulas	Use of indwelling lines
	Blood volumes Frequency Sampling regime	• Guidelines for safe volumes[1] • Engagement with clinical teams[1] • Consider alternative methods to reduce sample volume and number[2]- ○ opportunistic sampling ○ scavenged samples ○ other bodily fluids

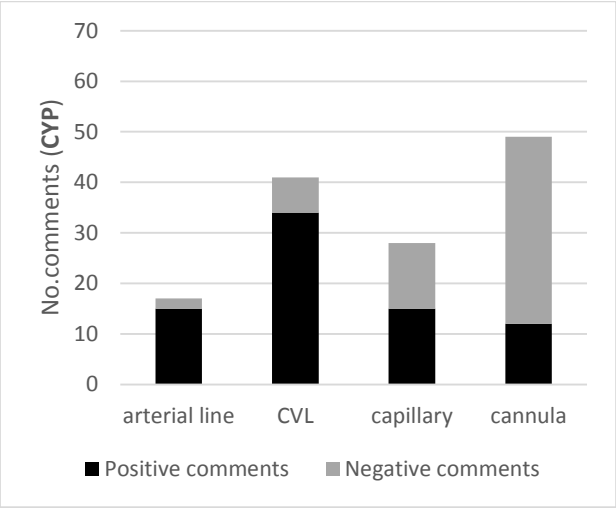
[1]See *6.3.4.3.7* [2] See *6.3.4.3.9*

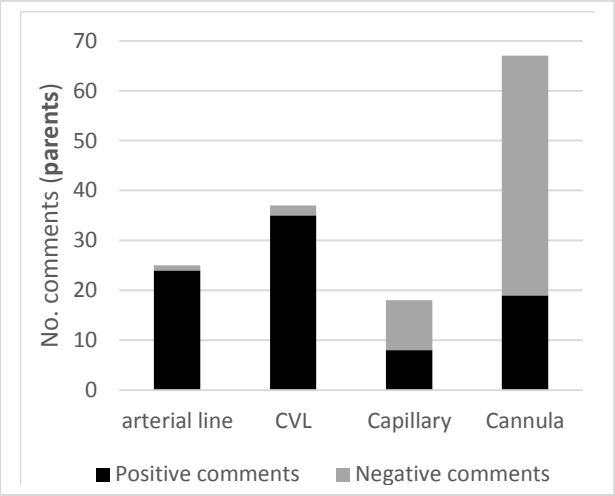
6.3.6.1 Barriers / challenges to sampling

6.3.6.1.1 Vascular access

Within the vignette different types of vascular access were discussed and compared. These included arterial lines, Central Venous Lines (CVL) and peripheral vascular access devices- cannula and capillary samples (see *Figure 32* below).

Figure 32: CYP and parents' attitudes towards vascular access





Overall capillary sampling, was unpopular with both groups. Negative comments reflected the side effects of the capillary sampling procedure, such as scarring and the distress associated with handling, pain and the squeezing action required:

> *"...you can still feel the scars, or still see the scars on his heels now. He had quite a few as you can imagine." (P-87; son was admitted to NICU as a new born)*

Sampling from a cannula was even more unpopular. Both groups commented that cannulas were painful, restrictive and also a source of distress for the CYP:

> *"…if you've got a cannula in the back of your hand… it's no good the nurse saying, "It can't be hurting you, it doesn't hurt." Or, "It's only plastic. It's not a needle in your arm. It's only a little bit of plastic." It's something alien to you, isn't it?" (P-113)*

There were also specific challenges to cannulation related to individual's anatomy and physiology, particularly those with a chronic condition or rare disease, such as smaller vessels, thickened skin or saturated skin secondary to renal failure. Both CYP and parents were cautious about who could undertake these tasks, recognising the additional challenges these features posed:

> *"The problem is I must have about three good veins in my body and that's it. Hopefully I'll be able to use that one there because I've got one there and one there (gestures location of veins) but they're really hard to find" (C-104)*

> *"you need someone who is very experienced at doing it... I have found in the past that it helps if it is the same person doing it every week because with their particular condition, their veins are a bit small and a bit wiggly and that makes it even harder. If you have got someone coming in as a one off, they are not going to have any previous knowledge of how easy or difficult it is to find a vein." (P-71)*

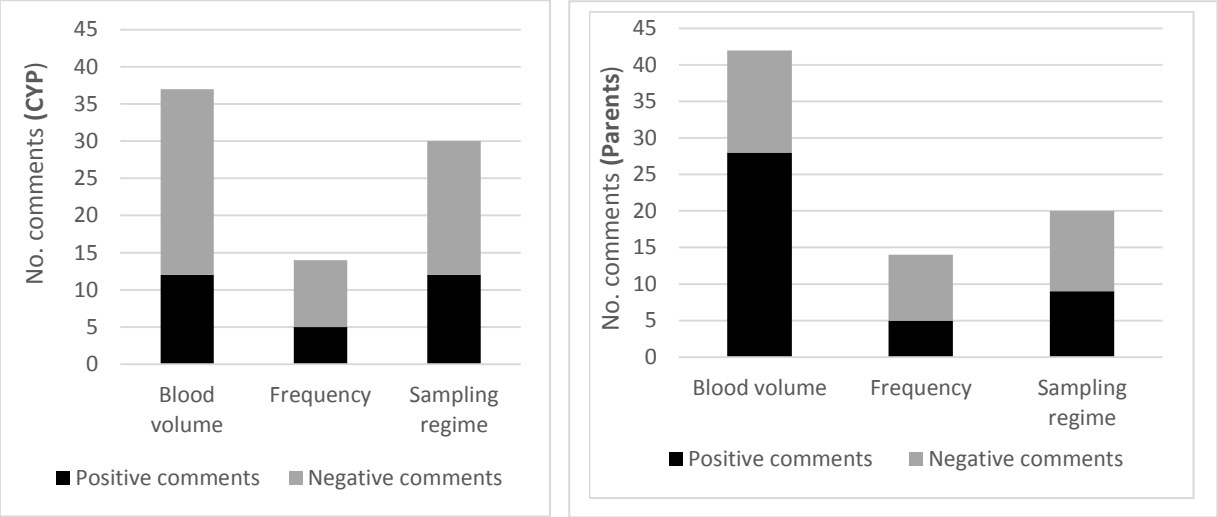
6.3.6.1.2 Obtaining samples

There were a large number of comments relating to 'obtaining samples', with three sub-themes: blood volume, frequency and the sampling regime (see *Figure 33* below). The volume of blood being sampled was the most commented on aspect by both groups; although parents tended to be more positive about the issue of blood volume than CYP.

Concerns (mostly from CYP) focused on safety, the impact of blood sampling, as well as the associated discomfort:

> *"They filled up five bottles from one arm on my blood test... I was there for like a good minute and that minute feels like, ages. You want to be over and done with not like sit there for five minutes pulling blood out" (C-82B).*

Figure 33: CYP and parent perspectives on study sampling requirements



Although the number of blood samples being taken did not appear to be a large concern for most participants, comments were predominantly negative. These reflected concerns about the number of occasions the CYP would be approached and the potential this gave for distress to the CYP:

> *"If you were doing it when she was conscious and there was an ordeal attached to it**, definitely** less the better." (P-114)*

The sampling regime appeared to be a greater concern for CYP and parents than the actual number of samples. Concerns reflected potentially disturbing the CYP whilst they were unwell and the specificity and restrictive nature of the protocol:

"if you came in and said I need to wake him up now to take that, I am not sure. I think my answer would depend on how the day had gone, because would I want you to wake him up if he had been awake for 6 hours? Possibly not." (P-89)

6.3.6.2 Facilitators associated with sampling

In contrast to comments about accessing peripheral vascular access or conducting capillary samples participants were extremely positive about the concept of sampling from indwelling vascular access. Arterial lines were viewed extremely positively by all participants with 15/ 17 (88%) comments positive from CYP and 24 /25 (96%) comments positive from parents on their use. CVLs were also popular- 34/41 (83%) positive comments from CYP and 35 /37 (95%) positive comments from parents. Positivity related to the fact that these devices were clinically indicated and there was no additional pain / discomfort involved in their placement:

"...it is in, it is not going to hurt them when you are doing it, it is already established, so I kind of think why not?" (P-89)

Several participants had port-a-cath's (permanent venous access devices) in situ and the placement of these had been a huge improvement from both a parent and child perspective:

"So, you know, before we had ports, we used to have cannulas. You know why we just changed to ports, because our veins …

Our veins wouldn't stand out" (C- 70A&B siblings discussing why they had port-a-cath central lines inserted)

As outlined in *6.3.4.3.9*, different approaches which reduced the sampling volume, the frequency of sampling or meant there was flexibility in the sampling regime were valued.

6.3.7 Processing

Overall CYP and parents did not recognise there to be many areas of concern related to the processing and interpretation of results from PK studies. See *Table 37* below.

Table 37: summary of barriers / facilitators to processing (CYP & parents)

	Barriers	Facilitators
Processing	Care taken with handling Documentation accuracy	Adequate staffing (research or clinical)

CYP reflected on the need for care with participants' samples to avoid waste and repetition.

> *"Really annoyed. So, I've also had like, they were taking, they dropped the blood. They actually dropped it on the tray and they had to take some more... They wouldn't like it if they had to do it." (C-82E)*

Parents in contrast were concerned about the accuracy of documentation required for a PK study and whether this would be to the standards required:

> *"Without implicating people, you probably can see this going on, yes I should have been here at 1 o'clock but it's actually ten past one. Mmmm, that's 1 o'clock. "(P-102)*

The main factor identified by CYP and parents to avoid / address issues with processing and reduction in waste was adequacy of staffing. With appropriate resources accuracy could be maintained.

6.3.8 Outcomes

6.3.8.1 Barriers / challenges associated with outcomes from PK research

'Outcomes' was used to collate codes equating to results, outputs or consequences of PK research. Key barriers and facilitators are outlined *Table 38* below.

Table 38: summary of barriers and facilitators related to study outcomes (CYP & parents)

	Barriers	Facilitators
Outcomes	Increased staff workload	• Research culture • Engage with clinical staff • Support from research staff • The right research design

6.3.8.1.1 Increased staff workload

Both CYP and parents had mixed feelings about the extent to which clinical nurses could be involved in research activities alongside clinical care. Although they were felt to be well-placed to assist with research activities, there was a recognition that this was not feasible.

Negative comments reflected concerns over their ability to comply with research regimes and requirements and a concern over adding to their workload

> *"Yes, I don't think they'd have the time or I think it would be delayed…I don't think it would work at all." (P-114)*

Both groups expressed concerns that this could diverting clinical staff away from key aspects of their job. The consequence being that not only could research conduct be compromised but clinical care could also suffer:

> *"Then you might think it might change your care. She's already got all these things to do and she's got all these things to do for research. It might put pressure on her and affect your care 'cos she's rushed" (C-117B)*

6.3.8.2 Facilitators associated with successful study completion

6.3.8.2.1 Research engagement and support

As identified in *6.3.4.3.7* engagement of research and clinical teams was regarded as essential at all stages of research conduct. CYP and parents were not concerned about additional people coming to the bedside to carry out research activity, provided there was clear communication about what they were there to do and how their role fitted alongside clinical care provision. Some parents commented that this would actually be a reassurance and perceived this as offering a higher level of care:

> *"...actually, I'm getting a double whammy because the research nurses are still nurses and should anything, God forbid, happen, they're not going to say. I'm going to stand back, I'm here for my research only … In an emergency situation, it doesn't matter, they're all going to work together" (P-108)*

6.3.8.2.2 Research culture

Many participants referred to the importance of research to improve health care. For some, this was related to a recognition that their child had benefited from previous research:

> *"It has also been explained to me that 20 years ago, nothing could have been done for *, so if somebody hadn't taken those first steps 20 years ago... and still in some parts of the world, babies born small like * was with these issues, they would say it's not possible. And yet * is a living example that it is." (P-86)*

Others could see that innovative work and research had been going on even whilst their child had been a patient, which was altering contemporary care and management. They therefore felt they were benefiting from fellow patients. Most people referred to research contributing to improvements for other CYP in the future:

> *"we wouldn't be where we are now without research. So, my personal view is the only way to go forward is research and if we can help, then absolutely" (P-105B)*

There was even some recognition of the issues faced in prescribing and using medications for children with three parents commenting on the use of off-label and unlicensed medications:

> *"most of *'s medication I noticed it says 'unlicensed' and that often makes me think, oh there's not been research into that medication used on children." (P-92)*

One child also reflected on a medication she was receiving and the concerns she felt about receiving it:

> *"Yeah… I just know that it's a highly toxic drug being administered. That kind of makes you think, "Hang on a minute. What are they injecting in to me?" Is it life threatening? It could be. If something went wrong with it or a wrong dose, this worries me a bit" (P-104)*

Understanding how care has been informed by previous research and how future care will be shaped was an important motivating factor for many CYP and parents. This information could be utilised to set the background and context to a PK study.

6.3.8.2.3 The right research design

Despite all the concerns raised throughout the interviews and focus groups, at the end of the session 18/22 CYP (82%) (4 CYP not specifically asked) and 17/18 parents (94%) said yes, they would consider participation in a PK study. Only four people (3 CYP and 1 parent) specifically said 'No', and three would reconsider this if the tests could be done on an alternative sample such as urine or saliva or on blood that had already been taken:

"If the people came and said that we could use the blood that's already been used, yes, 100% yes." (P-121)

This indicates that if a PK study is designed with CYP and parents' involvement, recruitment and study retention can be addressed.

In summary, there were high levels of support for research from both CYP and parents and this extends to consideration of PK research. Successful retention of participants in a PK study could be facilitated by engagement with clinical staff and the provision of research support as well as a research design which allows for the utilisation of scavenged samples or non-blood sampling.

6.3.9 Context

6.3.9.1 Barriers/ problems with the context of research

Participants made many comments reflecting the location or context of PK research conduct. (See *Table 39* below for a summary of barriers / facilitators).

Table 39: summary of barriers and facilitators to the context of research (CYP & parents)

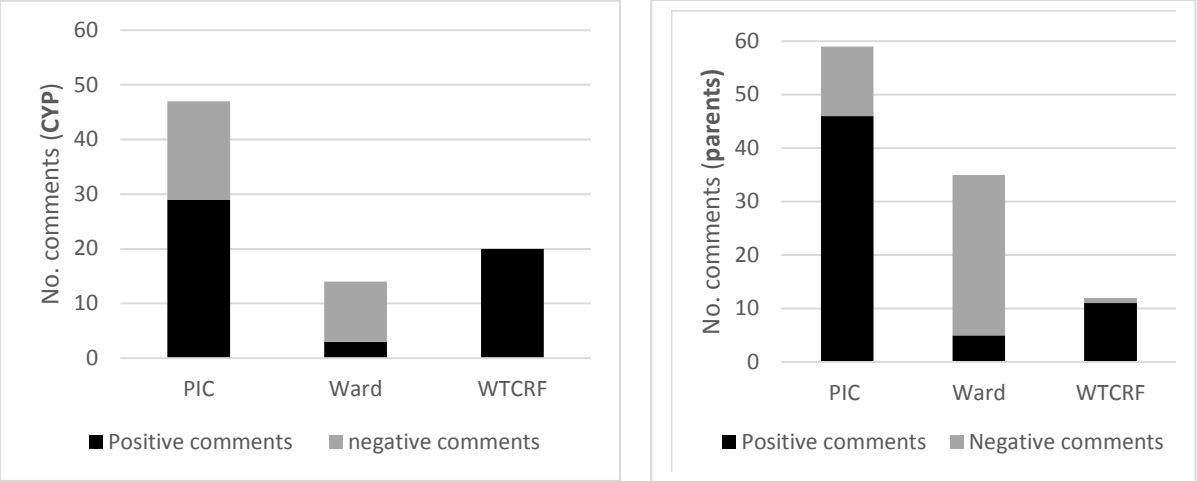
	Barriers	Facilitators
Context	Wards	• WTCRF[1]: outpatient basis • PIC: inpatient admission • Adequate staffing (research or clinical)

[1] Wellcome Trust Clinical Research Facility (WTCRF)

Figure 34 below summarises attitudes from both participant groups towards PK research in different clinical areas. Conducting PK research within ward areas was clearly felt to be problematic with concerns reflecting the demands of the environment and the staffing ratios:

"If you've got one nurse to four children, then that's a bit difficult especially if one has to have extra treatment done." (P-107)

Figure 34: CYP and parent attitudes towards the context of PK research



6.3.9.2 Facilitators associated with context

If a PK study was to be conducted on an outpatient basis, Wellcome Trust Clinical Research Facility (WTCRF) was felt by both CYP and parents to be a safe, appropriate place to do this:

> *"I mean here it's like they know exactly what they're doing, when they have to do it"*
>
> *"Yeah, they know exactly how to look after you and what ways to do it in" (Exchange between Participants C-70C and C-70D)*

It is worth noting that this was conditional on activity being conducted within office hours as overnight stays for research purposes were extremely unpopular with CYP. Many CYP and parents felt that PK studies could be conducted on PIC as children would have analgesia and sampling would be facilitated due to the presence of arterial or CVL devices:

> *"I think just do it in intensive care because it is the best time... And you're not really too aware of what's going on anyway, so it doesn't really affect you in any way" (C-75B)*

In addition, the staffing ratios of one: one staff: patient ratios would facilitate the timely conduct of study requirements. There were comments about the vulnerability of families

and the immense pressure they are under, but overall there was support for PK research within the PIC context.

6.4 Mapping to I-PARIHS

Using the integrated PARIHS framework (I-PARIHS) (Harvey and Kitson, 2016) the key aspects for the 'recipients' -CYP and parent groups- have been mapped out in relation to the 'innovation' PK research studies. See *Figure 35* and *Figure 36* below.

Figure 35: summary of CYP responses mapped to I-PARIHS

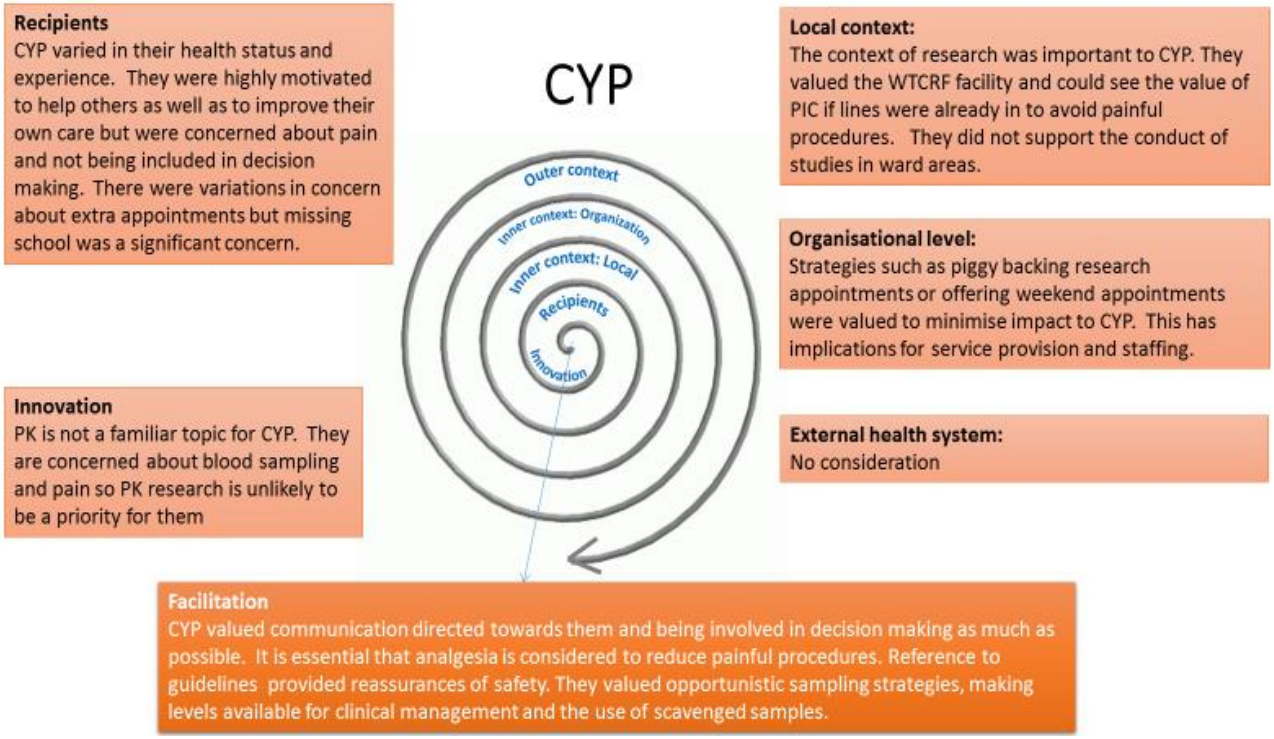
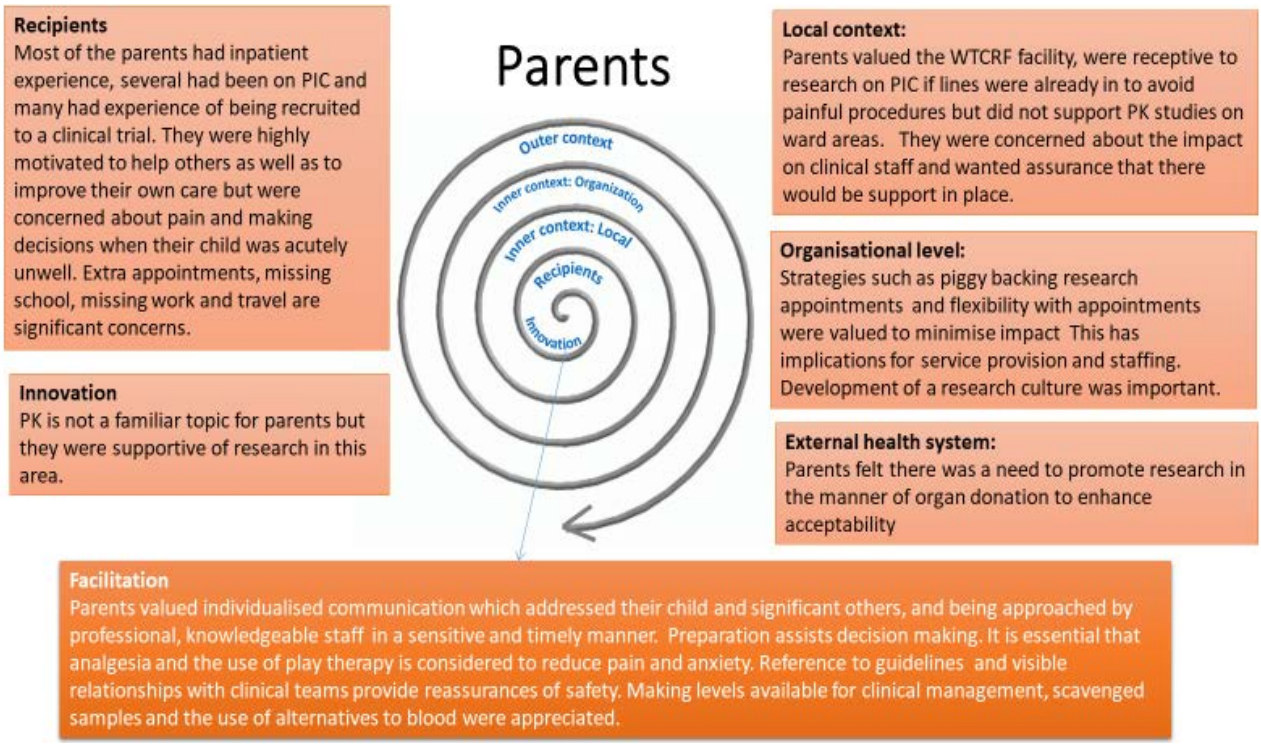


Figure 36: summary of parents' responses mapped to I-PARIHS



6.5 Discussion

6.5.1 Decision-making

There was a high level of congruence between the two participant groups about factors influencing decision making. The main motivation for both CYP and parents was altruism and to receive personal health benefits. This is in keeping with a systematic review of adults with emergency medical conditions (Limkakeng et al., 2014), a qualitative meta-summary of research with CYP and their parents about participation (Tromp et al., 2016) and a systematic review of consent to clinical trials with pre-term or sick neonates (Wilman et al., 2015); all of which highlight the top motivations for research participation as altruism and personal benefit. Despite the fact many PK studies offer no possibility of personal benefit from participation participants in PRESCRIBE indicated that they would be willing to consider participation in research. This is similar to Wendler et al (2012) who reported 90.4% of

adolescents and 91.6% of parents were willing to allow extra blood to be taken, even when it was of no direct benefit and may even tolerate minimal risk (Wendler and Jenkins, 2008). There is evidence that people can find meaning or benefit when researchers do not perceive there to be any. Patients with chronic health conditions can feel motivated by a strong sense of belonging to a particular group that would benefit from the research (Pletsch and Stevens, 2001, Limkakeng et al., 2014). In addition, individuals who have spent more time in research may have increased trust in researchers, increased comfort with research procedures and increased recognition of the value of research, so there may be gains which researchers themselves do not value (Wendler et al., 2012). Luchtenberg et al (2015) similarly found that there were subcategories to participation benefit, including improvement in dealing with their disease, getting closer attention and monitoring as well as learning about themselves and gaining confidence in managing their disease. PRESCRIBE provides evidence that CYP and parents will consider participation in paediatric PK research studies, motivated for personal benefit and to help others. This is consistent with literature that exists surrounding CYP participation in other types of research.

6.5.2 Consent rates

Two studies have explored the experiences of children with cancer participating in *optional* non-therapeutic studies, where patients will not benefit directly from inclusion. These studies were PK (Berg et al., 2010) and PK and pharmacogenetic (Errington et al., 2016). Both report high levels of altruism to help others and to help researchers learn more about the drug, with Berg et al (2010) reporting a consent rate to PK studies of 72%. Errington et al (2016) explored attitudes from 100 patients but it was unclear what the overall consent rate was. Participation rates to the theoretical PK study in PRESCRIBE were 82% CYP (18/22) and

94% of parents (17/18). Whilst these figures are encouraging and highlight support for PK research, the mean recruitment rates to PK studies identified in Chapter two were around 59%. It is therefore likely that these figures would be much lower outside of a 'theoretical' study.

6.5.3 Pain & distress

Most participants (CYP and parents) commented that additional painful procedures, particularly the insertion of a cannula, would mean declining participation. This is in keeping with other research studies which found that parent attitudes towards capillary puncture or venepuncture for research purposes were overwhelmingly negative (Seemann and Reinhardt, 2000, Jenkins et al., 2009, Abernethy et al., 2013). There was also a preference for strategies which minimised painful procedures and reduced waste. This is supported by studies in which parents rated the use of residual blood spots from new-born screening as their preferred method (Jenkins et al., 2009) or approved an extra sample taken alongside routine bloods (Freibott et al., 2016). In a US study of optional PK studies 83% of participants ranked it as very important that participation would not cause additional pain or harm to the child and 43% were concerned about the placement of an additional IV cannula for sampling blood (Berg et al., 2010). In a similar UK study, only 8% of parents and 9% of children felt that too many blood samples were taken (Errington et al., 2016). However, patients in this study had all samples taken from central lines which may have contributed to the positivity of parents and children towards participation. Participants in PRESCRIBE agreed with this approach, preferring that PK studies are conducted whilst the child has optimum pain management, is sedated and / or has a clinically indicated CVL or arterial line.

This means during admission to PIC is regarded as the optimum time, despite the associated stress PIC admission brings.

Avoiding or minimising pain was extremely important to participants from both participant groups in PRESCRIBE and the use of topical analgesia was advocated. This is well recognised as valuable in clinical care (Cordoni and Cordoni, 2001). A number of parents also referred to play therapy and distraction. Although there is reference to the use of these services in clinical care (French et al., 1994, McCarthy and Kleiber, 2006) there is no reference specifically to the research setting. Given the huge impact of pain and potential distress on decision making by the CYP and parents, future research design must consider the concept of invasiveness within a study protocol (Altamimi et al., 2016).

6.5.4 Involvement of the CYP

Involvement of children in decision making about participation in research was highly rated by CYP within this study. Previous studies have suggested that adolescents often abdicate decision-making to their parents (Hinds et al., 2005) but findings from PRESCRIBE are in keeping with a recent study of decision-making on participation in paediatric oncology, which found that adolescents preferred a collaborative role in decision-making (Ingersgaard et al., 2017). Although this was recognised by some parents, there was a marked difference between the extent to which this was a priority between CYP and parents. Age of the CYP was identified as an influencing factor but similar to the published literature (Broome et al., 2001, Abernethy et al., 2013) there were different suggestions from participants at what age involvement should start to occur. The Children's National Service Framework (Department of Health, 2003) states that all children should be consulted with and involved in all aspects of their care, including research. In addition, there are suggestions that being consulted,

leads to enhancement of wellness in children and positively influences health outcomes (Coyne, 2006). This seems to suggest that regardless of age, all CYP should be facilitated to be involved in decision making about research. Researchers need to ensure that the communication needs of both CYP and their parents are addressed, rather than making assumptions based on age. Without this there is the potential to cause conflict between CYP, parents and clinicians during the consent procedure.

6.5.5 Vulnerable groups & health status

CYP and parents recognised the need for PK studies to be inclusive in invitation to participate, however they had some reservations about the approach and recruitment of those they viewed as 'vulnerable'. Parents were more concerned about CYP who were not expected to survive, whereas CYP were most concerned about the inclusion of young infants, although they also had concerns about palliative patients. This concept of protecting vulnerable or critically ill populations from the demands of clinical trials has been noted amongst health professionals (Nicklin and Spencer, 2004, Macrae, 2009) and Research Ethics Committees (Kreicbergs et al., 2004, Angell et al., 2010). PRESCRIBE identifies that CYP and parents can also have strong opinions on research conduct and potentially oppose research with those viewed as vulnerable. This is despite the fact that parents can find research participation positive, even in times of bereavement (Dyregrov, 2004) and participation is rarely regretted (Newman and Kalouek, 2004). The evidence surrounding parents' attitudes to research with neonates and infants is less clear. In the Neonatal Intensive Care Unit (NICU) setting there is evidence that mothers of pre-term infants were twice as likely as mothers of term infants (48% vs 23%) to consider participation in a research study (Maayan-Metzger et al., 2008). However in a study of consent rates to research in the PIC setting,

there was a trend toward lower consent rates in younger children and also in those undergoing cardiac surgery (Menon et al., 2012). It appears that within the neonatal setting parents might be more willing to consider research when their child is premature and /or low birth weight, whereas in PIC being younger or having a congenital problem such as a cardiac anomaly might make parents *less likely* to participate (Slosky et al., 2014). This would seem to support the finding within PRESCRIBE that neonates were viewed with concern. However, in none of these situations is the concept of immediacy in the critical care setting addressed.

CYP and parents in the PRESCRIBE study commented that decision making about research during a perceived life-threatening episode was difficult. Within the adult literature this acuity was actually highlighted as a reason to participate as participants did not want to delay treatment (Limkakeng et al., 2014). However similar to Morris et al. (2007), participants in PRESCRIBE were concerned that participation in research might divert the clinician's attention from their child. The hypothetical requirement to make decisions quickly challenged many of them and the default position seemed to be to decline, rather than consent to research, which has implications for research studies with a time sensitive eligibility. A PIC admission is known to be incredibly stressful for parents (Colville et al., 2009) and being too stressed to make a decision has been identified as the biggest reason for declining participation in PIC studies (Menon et al., 2012). Morris et al (2007) also found there was a far lower level of support for research in emergency situations than research in non-emergency settings, although it was not clear whether it reflects a perception that such research is not valuable or whether it is not appropriate. Parents in PRESCRIBE could see a place for research in emergency situations but concerns seemed to focus around

appropriateness, particularly when the vignette highlighted a time limited situation and also the concept of uncertainty. This seems to suggest that conducting PK research in a time-sensitive situation, with infants, admitted to hospital in a critical condition could be particularly challenging.

6.5.6 Facilitators: communication and the approach

One of the biggest facilitating factors for CYP and parents within PRESCRIBE was effective communication, particularly at the recruitment stage. Families rated communication as one of the most important skills of physicians, especially during critical illness (Meyer et al., 2006). Research staff need to gauge the right level of communication and for each individual family. Families are more likely to participate if they have a greater understanding of study concepts and study specifics (Tait et al 2003, Hoberman et al 2014). Studies have also shown that subjects who were well-informed and received adequate communication also had better compliance and a reduced premature withdrawal rate (Lynoe et al., 1991). Communication therefore has an important impact on recruitment and study retention. However, CYP and parents within PRESCRIBE also highlighted that recruitment is reliant on more than just communication skills, particularly at the stage of initial contact. Crucial elements included professionalism, tact, courteousness as well as communication elements such as clarity and provision of appropriate information. This view of the researcher is crucial because positive parental perception of the researcher is associated with greater likelihood to assent (Tait et al 2003, Hoberman et al 2014), particularly at the initial encounter (Perez et al 2010). Mothers of diabetic children similarly defined a 'good paediatric researcher' as approachable, responsive and dedicated (Pletsch and Stevens, 2001). These are key aspects researchers can focus on to improve the recruitment process.

One of the biggest challenges for researchers in neonatal settings is approaching families at an appropriate time (Wilman et al., 2015). This is also reflected in PRESCRIBE participants' concerns about approaching families about PK studies in a PIC setting. Liaison and close partnership with health colleagues is recognised as effective to enhance recruitment to trials (Gooch, 2000, Wilman et al., 2015) and helps to reduce inappropriate and poorly timed approaches. Knox and Burkhart (2007) also suggest that developing relationships with colleagues can lead to improved referral and potential recruitment as the CYP and family trust and respect their health care provider's opinion. Researchers therefore need to demonstrate a visible relationship with clinical colleagues and ensure the timing and approach are optimised.

6.5.7 Personal impact

Extra visits to hospital were a huge concern for parents within PRESCRIBE, with the associated implications of missing school, work, travel and parking costs. Indeed spending extra time in the hospital was identified as a reason by 50% of those who declined participation in a PK study (Berg et al., 2010). Research highlights that when a child participates in research much of the burden falls on the shoulders of parents, including hospital attendance, work absences and research requirements to complete paperwork. These can be hugely draining for parents (Tromp et al., 2016). However, children also feel the impact of research as a burden (Pletsch and Stevens, 2001, Hein et al., 2015). Strategies for reducing this burden for CYP and families could include on-line visits and telephone interviews to reduce the burden of research visits. Indeed 83% of parents in an ED study would consent to a study that involved a telephone follow up. This figure reduces to 58% when an additional appointment is proposed (Abernethy et al., 2013). Preferred options

raised by CYP and parents in PRESCRIBE were flexibility, with suggestions of after school or weekend appointments and home visits. This is supported by Knox & Burkhart (2007) observation that the single biggest factor for retention of children in research studies is to allow for flexible scheduling. Volmer et al (1992) found that scheduling clinic visits in the late versus the early afternoon resulted in better participant attendance. Saturday appointments were identified as useful for some participants but were also the most commonly missed appointments. However, the most preferred option amongst participants in PRESCRIBE was to 'piggy back' appointments to clinically indicated appointments, so clinical and research care are conducted side by side. There are no published accounts of this to allow the evaluation of the utility and cost-effectiveness of such a strategy. This requires further exploration. The message overall was that CYP and parents felt the impact of clinical care and are reluctant to add burden through research participation. The best strategy was to avoid extra demand altogether.

6.6 Limitations

6.6.1 Participants

There were multiple sibling pairs interviewed together (at the family's request) which may have influenced respondent's answers. However, the presence of a sibling was sometimes useful to add clarity or to remind the other of a specific occasion. Interviews were held at the participants' homes so it was also difficult to exclude parents from the process, although they were discouraged from being present and participating. One interview was cut short when a clinical situation occurred during a child's clinic visit. A follow-up time to complete the interview was unable to be scheduled as both the researcher and the parent were then on maternity leave.

The CYP who had experienced PIC were knowledgeable and insightful but there were low numbers interviewed. In part, this was because there were low numbers of eligible CYP to interview, but in addition, there were a number who declined at the point of invitation and after being discharged home. Purposive sampling of CYP with experience of clinical trials was more successful. However, for some the visits to the hospital had come to be their way of life, so caution is required in the interpretation and transferability of the results to a wider population.

6.6.2 Subject matter

PK research as a concept was deemed 'complicated' by the PPI participants, particularly for CYP. Despite the use of props and aids and the vignette, it was unclear at times if participants had understood the questions fully or if things were not important as their answers were limited in depth. To overcome this the researcher did summarise responses and check participant agreement and was satisfied with comprehension. The use of the vignette was also valuable as it enabled the discussion to remain focused, particularly when exploring alternative methods for conducting PK research.

There were some situations where not all participants were asked the exact same questions. Participants were purposively sampled to have a wide range of experiences and it seemed illogical to press participants to discuss research care in WTCRF when they had experience of care on PIC and vice versa. For transparency, response rates are reported to enable the reader to see where this is the case.

6.6.3 Interview conduct

A purposive sampling strategy of parents of children who had experienced PIC or clinical trials meant that many were parents of children with complex health conditions. Timing of

interviews was extremely challenging. Conducting them whilst the CYP was still in hospital meant interviews were frequently postponed due to changes in the child's clinical condition. In addition, parents were anxious about leaving their child. Conducting interviews once families were discharged, meant some then failed to respond to contact or there were challenges about arranging home visits around parent's work and other commitments. This therefore did lead to some families not responding to follow up.

6.7 How does this qualitative work with CYP and parents address the knowledge gap surrounding pharmacokinetics?

This chapter set out to address gaps in knowledge associated with the service user perspective, the influence of context and facilitation and has addressed all three aspects.

1. There is a paucity of research conducted with CYP to understand their views on research and trial design generally and within the PK literature very little was known about attitudes of CYP and parents. Where research had been conducted it was specifically related to PK in phase 1 /Phase 2 studies in oncology (Berg et al., 2010, Errington et al., 2016) or a study in CYP with Attention-Deficit Hyperactivity Disorder (Fogas et al., 2001). This is the first study to address the subject of PK studies outside of a specific diagnosis or speciality and utilise face to face methods to conduct the research. New knowledge has been gained to show the negative influence of additional painful procedures and additional hospital appointments on the decision to participate in PK research. In addition, there is a clear discrepancy between current PK study protocol recommending the placement of a peripheral cannula for sampling and participant's expression of this as their least preferred method. Factors such as the influence of blood volume, the number of samples and the sampling regime and new

approaches for conducting PK research have not previously been explored. PRESCRIBE therefore provides insight into the feasibility and acceptability of novel study design.

2. This is the first study to explore the influence of context and the considerations of conducting PK research in an emergency / intensive care environment. Historically there have been concerns about approaching families to consider research, particularly when CYP are acutely ill (Kanthimathinathan and Scholefield, 2014). However, PRESCRIBE has found that CYP and parents will not only consider research within the PIC context, but may actually prefer it to take place in this context when their pain is well controlled and they have vascular access for sampling. There are also important messages about the value of designated research areas for research conduct. There is little formal evaluation of the roles and utility of facilities such as Wellcome Trust Clinical Research Facilities. PRESCRIBE provides evidence that these are an important resource for CYP and families in the context of PK studies.

3. The third gap in the knowledge PRESCRIBE addresses is the identification of facilitators to aid researchers with future study design and conduct. PRESCRIBE has systematically reviewed all stages of the PK research process, identifying not only barriers and challenges at each stage but also enabling factors / facilitators to overcome these. These facilitators address psychological, social, emotional and financial needs of CYP and parents. Recruitment and retention to paediatric studies is recognised to be challenging (Caldwell et al., 2004, Tishler and Reiss, 2011, Menon et al., 2012). With enhanced understanding, measures to assist with research conduct can address both PK recruitment and study retention.

6.8 Conclusion

Conducting interviews and focus groups with CYP and parents was a challenging undertaking, requiring reflexive sampling and study methods. Valuable information to inform the design of future research was obtained. CYP and their families will consider participation in PK studies, even when there is no direct benefit to themselves, provided there is minimal or no additional painful procedures, or analgesic measures are put in place. Ideally this type of research will take place when CYP are inpatients, with clinically indicated intravascular access in place for sampling. Provided there is sensitivity to the circumstance and the timing of approach PIC is regarded as an optimum time to carry out this type of research. CYP and parents prefer strategies which minimise the disturbance to them such as samples taken alongside clinical care and scavenged samples or would like the results to be made available to clinicians so they feel they have 'gained' from their involvement. Overall CYP and parents are willing to consider participation in PK studies, although this may depend on the medication under investigation and the perceived benefit for their clinical condition.

Chapter 7: Exploring the attitudes of nursing staff towards Pharmacokinetic studies in critically ill children

7.1 Introduction

7.1.1 What is known about clinical staff attitudes towards pharmacokinetic research?

There is evidence that clinicians can heavily influence recruitment to research through expressing their preferences (Mansour, 1994) and non-invitation of potentially eligible patients (Nicklin and Spencer, 2004). Amiel et al (2007) reported not inviting eligible paediatric patients, driven by ethical concerns related to the study design, the severity of the underlying disease and anticipation of families refusing to participate. Shilling et al (2011) also found that practitioners can regard approaching families about trials as an unwelcome burden and some felt personally uncomfortable and awkward about recruiting children to trials. This reluctance of clinicians to participate can be a greater obstacle to successful completion of a trial than the reluctance of patients (Fallowfield et al., 1997). However, the majority of this work has been undertaken with adults and within the oncology field. Little research has taken place surrounding attitudes towards research in trials of medications.

There is some evidence that health care professionals may not recognise that the medications they are prescribing are being prescribed off-label (Chalumeau et al 2000) which is of concern. However other studies show that health care professionals are aware and are concerned about the safety (77.8%) and the efficacy (87.9%) of unlicensed / off label prescribing in children (Mukattash et al., 2011). Despite these concerns though, there can be a reluctance to undertake trials of medicine in children (McLay et al., 2006). Reasons for this

reluctance were unclear but are concerning given that clinical trials of medications are dependent on support from clinicians.

7.1.2 What is known about nurses' attitudes towards pharmacokinetic research?

Nurses occupy a key role in the contemporary drive to develop and maintain evidence-based health care across the UK (Department of Health, 2006). There is evidence to suggest that nurses have positive attitudes towards research, however the research in this area has tended to focus on exploring barriers to research utilisation and implementation (Nilsson et al., 1998, Bjorkstrom and Hamrin, 2001, Snelgrove and James, 2011). Paediatric nurses can be present at the time of recruitment of patients to trials, be involved with data and sampling collection and the following of trial protocols (Knox and Burkhart, 2007). However, little is known about the attitudes of clinical nurses towards research, particularly studies with pharmacokinetic (PK) sampling requirements. Chapter 7 aims to address the gap in knowledge related to clinical nurses' attitudes towards PK research, explore the influence of context on nurses' attitudes and identify facilitators (see Figure 37 below).

Figure 37: identifying gaps in the knowledge- nurses

7.2 Research aims

The aim of this work was to determine the attitudes of nurses working in a Paediatric hospital setting, towards paediatric PK studies, identify what they perceived to be a barrier or problematic about the conduct of paediatric PK research studies and identify what nurses identified as enabling or facilitating the conduct of PK research studies. Please see Chapter 2 for full details of the methods undertaken.

7.3 Results

7.3.1 Demographics

Recruitment to focus groups and interviews took place between 01.04.2013 and 28.02.2014. At the time of the initial approach in April 2013 the total number of eligible staff (Registered Nurses) on each ward (Band 5-8) was: PIC- 272, Ward 11 (Cardiac)- 30, Ward 12 (Cardiac)- 30, Ward 8 (Liver)- 30, Burns ward- 25.

26 PIC nurses from a UK PIC and 7 Ward Nurses (Burns Ward, Liver Ward and Cardiac wards) (n=33) participated in five focus groups (n=29), two interviews with two participants (n=4) and one to one interviews (n=4). One focus group (4 cardiac staff) had to be excluded due to poor sound quality, therefore total number of participants = 29 Registered Nurses. Participants included Band 5 (n=18), Band 6 (n=4), Band 7& 8 (n=7), with 15months -18years PIC experience. Participants are summarised in *Table 40* below, which features their place of employment, gender and level of paediatric experience. * Indicates nurse had undertaken Good Clinical Practice (GCP) training (n=3)

Table 41 provides details on the codes used within *Table 40*. Quotes from nurses are cited as N- individual study number. If this was conducted as part of a FG there is an additional letter to differentiate participants.

Table 40: summary of nurse participants' age, gender, band and experience

Participant	Age	Gender	Band	Department	Paeds experience	PICU experience	Method
49	2	F	5	PICU	2	2	Interview
57A	2	F	5	PICU	2	2	FG 1
57B	2	F	5	PICU	2	2	FG 1
57C	1	F	5	PICU	2	2	FG 1
57D*	1	F	5	PICU	2	2	FG 1
57E*	4	F	6	PICU	4	4	FG 1
57F	2	M	5	PICU	2	2	FG 1
61A	4	F	7	PICU	3	3	FG 2
61B	4	F	7	PICU	5	5	FG 2
61C	4	F	8	PICU	5	4	FG 2
61D	5	M	8	PICU	5	5	FG 2
61E	2	F	7	PICU	3	3	FG 2
73	5	F	7	PICU	4	4	Interview
74	5	F	6	PICU	5	5	Interview
80A	4	F	7	PICU	5	5	Interview with 80B
80B	3	F	6	PICU	4	3	Interview with 80A
98A	2	F	5	PICU	2	2	FG 3
98B	2	F	5	PICU	2	2	FG 3
98C	2	F	5	PICU	2	2	FG 3
98D	1	F	5	PICU	2	2	FG 3
98E	3	F	5	PICU	2	2	FG 3
98F	2	F	5	PICU	2	2	FG 3
106A	2	F	5	PICU	2	2	FG 4
106B	2	F	5	PICU	2	2	FG 4
106C	2	F	5	PICU	2	2	FG 4
106D	3	M	5	PICU	3	2	FG 4
97*	2	F	5	Liver	2	0-ward	Interview
99A	3	F	6	Burns	4	0-ward	Interview with 99B
99B	1	F	5	Burns	2	0-ward	Interview with 99A

** Indicates nurse had undertaken Good Clinical Practice (GCP) training (n=3)*

Table 41: codes for nurses' age and level of experience (in Table 42)

Age	Experience
1= 21-24 years	1= </=2 yrs
2= 25-29 years	2= >2 years- 4.99yrs
3= 30-35years	3= 5- 9.99yrs
4= 36-40years	4= 10- 14.99 yrs
5= 41-50 years	5= >/=15 yrs

All participants (n=29) had experience of PK in clinical practice and most were able to provide examples of medications that required levels taking as part of routine care. 4/29 (14%) had experience of sampling PK levels as part of a research study. However, only 13/ 29 (45%) were able to define what they thought pharmacokinetics was, possibly reflecting a lack of confidence in the terminology:

> *"I suppose I have not heard it in those terms before but I mean, you know, it is about how the drugs react in the body is what I would think" (N-73)*

Participants could however provide a variety of clinical applications of PK in practice. This seems to indicate that they understand the principles of why PK is of importance clinically, particularly senior staff (Band 6-8).

> *"That's why we have our liver protocols for things like paracetamol where you give the patients a reduced dose because they can't break it down as efficiently as if they hadn't had a transplant" (N-57B)*

7.3.2 Themes

Coding was condensed to the six core themes referred to within chapter 6.

7.3.3 Attitudes of nursing staff

During discussions about PK research conduct, nurses were relatively positive about the concept of PK research and generally rated families as having a positive attitude towards research (see *Table 42* below).

Table 42: summary of nurses' attitudes towards PK research with CYP

Positive comments (76%)	Negative comments (24%)
• Inclusive approach • Families value choice & opportunity	• Vulnerability • Experimentation • Health status • Impact on staff

Nurses felt many families would appreciate, or at least consider the choice and opportunity of participation:

> *"I've never had a parent complaining or say that they want to withdraw from a trial or anything like that and especially from parents whose children have passed away" (N-49)*

However, they also identified that some families will have concerns over the vulnerability of their child, being approached during critical illness, the concept of experimentation and the impact of protocol requirements on staff:

> *"I think that they won't see the value of the overall goals of the study. They'll just think what it comes down to is them personally having to do **extra**... in an environment where morale is not particularly high." (N-62C)*

Despite recognising the importance of families' views, there were very few comments about the views of CYP towards research or the importance of researchers involving or considering the views of CYP in discussions about research.

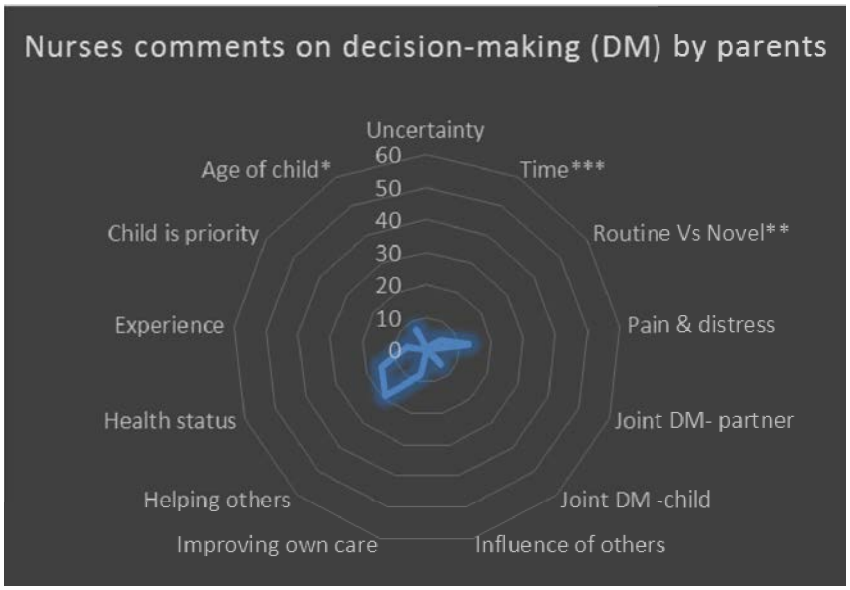
Overall despite large numbers of negative comments about the potential challenges of conducting PK research alongside clinical practice, all nursing staff were willing to support a PK study (see section *7.3.8.2.3)*

7.3.4 Recruitment

7.3.4.1 Nurses' perspectives on parents' decision-making

One of the most discussed aspects within Chapter 6 was factors which influenced decision making by CYP and parents about participation in research. Some of these factors were also raised by nurses, although there were far fewer comments overall (see *Figure 38* below).

Figure 38: number and distribution of comments on parental decision-making (DM) by nurses



*__Age__ was discussed in more detail but with regards to safety of sampling rather than in relation to decision making about participation

**__Routine Vs Novel treatment:__ The vignette was described as a 'routine' medication, rather than a 'novel' treatment. Only one participant made any comments about rare diseases and novel treatments.

***__Time:__ there were references to 'time', but all in relation to the nurses' time to undertake the research, rather than time required by participants to consider recruitment.

1. Helping others

The motivation of CYP and their families to help others was referred to by 14 nurses, the most commented on factor influencing decision-making. Nursing staff felt there was a high level of altruistic feeling towards research amongst parents, even when they were in an area such as PIC:

> *"Parents like to feel like they can help or prevent another child going through something. Parents feel quite helpless in those circumstances so the idea of actually helping by giving consent is usually something that really benefits them." (N-98A)*

2. Health status

A number of staff commented on the influence of the child's health status at the time of being approached for research. Some comments focused on the challenge for parents having to make a decision when their child was extremely unstable. However, others recognised that the reason for the child's admission could impact on whether the CYP could

actually participate, for example whether it would be possible to site a peripheral vascular access device if the CYP was shocked and peripherally shutdown:

> *"I think it would be difficult for most of our patients because they come in shut-down and with circulatory collapse and we've got difficulty with access anyway" (N-49)*

3. Pain and distress

Eight nurses recognised the pain and distress associated with invasive procedures such as blood sampling. Comments reflected that CYP and parents could experience concerns about additional requirements which could influence their decision-making:

> *".. there are so many kids that come in to outpatient's clinics now that literally because they've had so many bloods taken, so many stabs, so many times with cannulas, they literally scream as soon as they come in because they just don't want to be there…" (N-57B)*

4. Improving personal care

A number of nurses felt parents were motivated to participate in research as an opportunity to improve the care of their own child:

> *"Parents, I don't think anyone would say no, really, to improve their child's care." (N-98B)*

Some felt that even when there was no immediate direct benefit, some parents would still consider research, recognising their child could benefit during a future admission to hospital or in their future management.

7.3.4.2 Barriers to recruitment

The factors that influence decision-making by CYP and parents were not widely discussed by nursing staff. However, where comments were made there was a recognition of the altruistic nature of many parents. Other perceived barriers and facilitators are summarised in *Table 43* below.

Table 43: summary of barriers and facilitators to recruitment (nurses)

	Barriers	Facilitators
Recruitment	Vulnerable patients, particularly Infants	• Personal benefit to research • Benefit for others • Education / training • Safety -Education and training of staff -Reference to guidelines • No additional samples /sampling procedures
	Severity of health status	Deferred consent[1]
	Pain / distress	Use of indwelling lines for sampling[2]
	Safety	

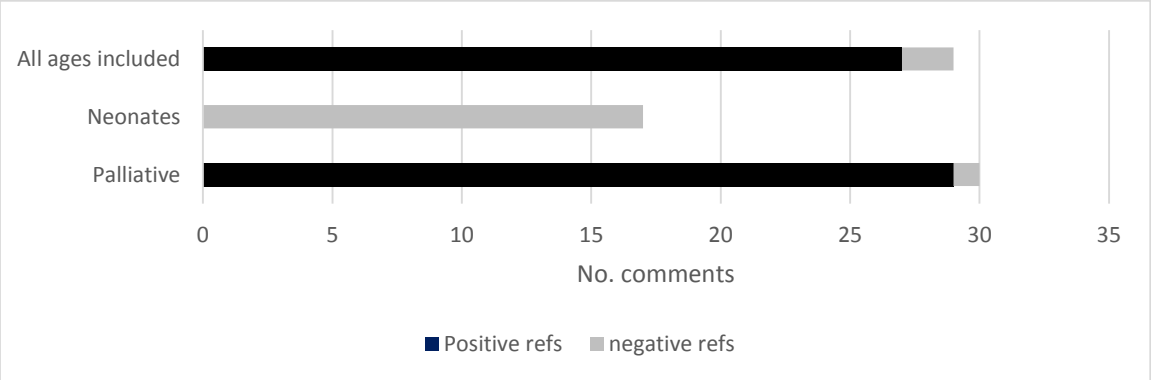
[1]Discussed in section *7.3.4.3.3*, [2] Discussed in section *7.3.6.2.1*

7.3.4.2.1 Vulnerable study participants

Nursing staff were generally supportive of broad inclusion criteria (see *Figure 39* below). Although age was not felt to be grounds to exclude patients from a study, neonates were raised as a concern by 12 people, with two people specifically stating they should be excluded:

> *"But if you've got a little weeny one, like our ITU one and you're taking that, it's quite a significant amount, isn't it?" (N-99A) (ward nurse)*

Figure 39: vulnerable study participants': nurses' views



There were no blanket comments about exclusion for patients who were not expected to survive or who were on a palliative pathway. In fact, the majority of comments (29/30) were positive to inviting them to participate, recognising that participation might even offer a

form of benefit. However, this was cautioned with the need to liaise with clinical staff about all patients; both to check if inclusion was clinically acceptable and also to determine the appropriateness and timing of the approach:

> *"I think in some families it might be that if you came in at that point that you might completely derail all the withdrawal talks, so I think it is just about having some form of liaison" (N-61E)*

There was also a recognition that palliative care could mean different things for different patients and families and did not necessarily mean the CYP was going to die imminently:

> *"You are going to get some parents whose kids are on this palliative care pathway, but they have been on it for five years. They know this is going to happen and they are prepared and they are not jolly, but they are accepting of it, so you could approach them." (N-106D)*

7.3.4.2.2 Hospital appointments

All the nurses interviewed worked on inpatient wards, with the majority (26/29) on PIC. Participants were asked about the impact of a PK study on families but there were no specific mentions of factors related to the impact of extra appointments, school, work and travel.

7.3.4.2.3 Summary of barriers to recruitment

There was a recognition that research staff should take an inclusive approach to patients on the basis of age and diagnosis, although liaison with clinical staff (identified as both medical and nursing staff) was vital to check individual circumstance. Decision-making was felt to be negatively influenced by the potential for pain and the requirement to make decisions at a time of deteriorating health status but overall there was less consideration about recruitment than from CYP and parents.

7.3.4.3 Facilitators to recruitment

7.3.4.3.1 Emphasise the potential benefit of participation

Although there were few blanket rules of exclusion, many nurses were concerned about the inclusion of neonates in PK research which offered no personal benefit. To address this a study would ideally offer some form of benefit to the CYP participating or would outline the benefit for CYP in the future

> *"If they think they're contributing to something that might not make a difference to their child at that moment in time, but for children in the future, they don't have a problem." (N-80A).*

7.3.4.3.2. Reassurance of safety

Safety of the research study for the individual patient was paramount to nurses. Two key components to this were the education and training for staff and reference to guidelines or standards. Education and training were crucial to ensure staff understood the purpose behind the study, what they were required to do and what to do in the event of any problems:

> *"It took quite a lot of drilling in how much you need to take and which bottle to put it in and it was very much 'this is an idiot's guide'... And there is definitely a place for idiots' guides for things" (N49) [Talking about a trial which involved a very specific management plan]*

18 people made reference to the value of guidelines to provide guidance on safe volumes for sampling, particularly if there were stratifications identified for different ages and /or weight groups:

> *"...as a bedside nurse it's drilled into you about protocols, procedures, prescriptions... and you've got something in front of you that says it's safe to take X, Y, Z amount of blood off a 3-kilo patient, then it would make you feel very slightly more comfortable about the responsibility of doing that." (N-73)*

7.3.4.3.3 Alternative approaches to PK conduct

In order to overcome issues and concerns associated with the sampling requirements of a traditional PK study alternative approaches were discussed. *Figure 40* below summarises

nurses' attitudes towards a number of alternative PK methods. *Table 44* then summarises the top four approaches.

Figure 40: alternative approaches to conducting PK studies (nurses)

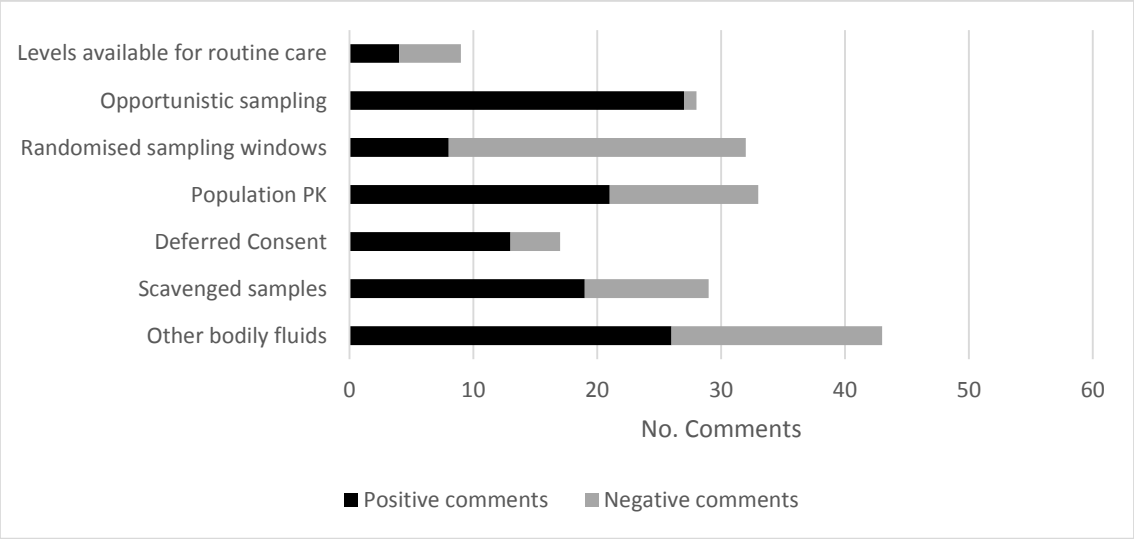


Table 44: top 4 preferences for alternative approaches to PK study conduct (nurses)

Nurses preferences
1. Opportunistic sampling
2. Deferred consent
3. Scavenged samples
4. Population PK

1. Opportunistic sampling

PK samples taken alongside routine bloods or as clinical need dictated was the highest rated approach, with 96% of comments from 20 staff positive. Nurses felt this reduced the infection risks associated with accessing lines and also minimised any extra work as it was taken alongside 'normal' care:

> *"I don't think it's unreasonable for us to assist when we are doing routine bloods and I think that you know just filling an extra blood bottle, nobody has got a big problem with" (N-74)*

2. Deferred consent

Deferred consent was discussed in the context of an emergency situation or the need to start a 'routine' medication quickly. A sample would be taken prior to administration as well as 'post' samples, until discussion with the family and informed consent could be obtained. Overall staff were supportive of this approach, with comments reflecting the fact that families would struggle to concentrate on any discussions at this difficult time.

3. Scavenged samples

Many nursing staff (n=15) approved of the idea of using blood 'leftover' after routine tests had been conducted and which would normally be disposed of as clinical waste for measurement of PK levels. Support reflected the fact this was not adding to nursing workload and avoided 'waste':

> *"I see no reason why they wouldn't really, because it is only going to get discarded if it's not needed for anything else. So, I see no reason why they would" (N-73)*

Where there were negative comments, these related to the question of why there was additional blood left after routine tests:

> *"It certainly raises issues with me because I never knew there was blood left over. Why are we taking all that blood when they are throwing it in the bin?" (N-106D)*

4. Population PK

Population PK approaches which are facilitated by sparse sampling methods were as a whole viewed positively. Nurses liked the idea of fewer samples per patients. They also thought families would prefer this approach:

> *"I think you're more likely to get patients and parents... signing up for four samples than... for the other regime where you're looking at seven or eight" (N-80B)*

However, negative comments reflected concerns about the accuracy and completeness of data. If there were any doubts, they preferred traditional methods with smaller numbers of

patients contributing more data, conducted with full supervision, to ensure patients' data did not go to waste:

> *"So as long as it was scientifically valid and we knew we could get the answers so that data didn't go to waste" (N-98D).*

7.3.4.3.4 Summary of facilitators

Nursing staff were reassured by approaches to PK sampling which avoided additional blood sampling or made use of samples that were already taken. The optimum study design would ensure there was some form of personal benefit for patients or emphasised the value for future patients. In emergency or time-pressured situations nurses were supportive of deferred consent for PK research.

7.3.5 Medication

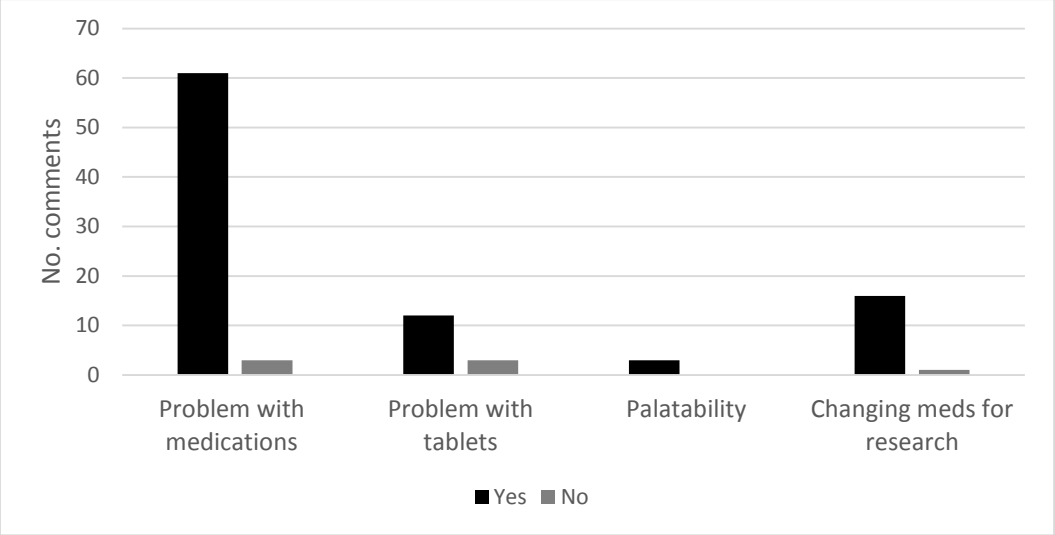
7.3.5.1 Barriers / challenges with medications

Nurses were asked about their experiences of prescribing and administering medications to CYP. There were 61 comments made by 23/29 participants; making it the second most commented on topic by nursing staff. The majority of these comments reflected problems / challenges (see *Table 45* below). The volume of comments about these issues are summarised in *Figure 41*.

Table 45: summary of barriers and facilitators to medication administration (nurses)

	Barriers	Facilitators
Medications	Accuracy with administration	• Training • Trial paperwork • Research support
	Tablets/ palatability / changing for research	

Figure 41: experiences and attitudes towards medications (nurses)



There were references to the challenges of monitoring medication levels even as part of routine patient management, with staff concerned about the potential for both under- and over-dosing patients:

> *"I think we probably under dose a lot of children, particularly antibiotics I would have thought because ...you are not necessarily alerted to the level. So, if you are busy, you might not get the level until a couple of hours after and I think kids end up having doses delayed" (N-61C)*
>
> *"I find the opposite – I think that we overdose a lot of them because we don't take into account their renal function and when you get a high level back obviously, you've given them the next dose anyway" (N-61D) (Dialogue between two ANPs on PIC)*

Other issues affecting the timely administration included: staffing levels, workload and patient acuity, medications prescribed for 'busy times', intravenous access availability, multiple and competing drug requirements, staff having the skills to administer medications and waiting for medical team input. Staff also identified issues about where PK measurements would be obtained from, particularly with limited vascular access which could create issues for both the administration of the medication (if IV) and sampling:

"You may have to prioritise drugs over other drugs as well. A drug that's once a day versus one that's four times a day, you might have to prioritise getting that one in first and maybe not start the study one at that time." (N-98A)

There were also specific issues for oral medications, including 'nil by mouth' status, patient refusal and difficulties with compliance. Despite these concerns there were comments that changing medications might not be appropriate. Some felt CYP and parents had strong preferences and would therefore be resistant to change, others commented that there may be safety issues changing from one formulation to another:

"We have seen it on the unit where different drugs – the same name drug – is given in a different form and it is less effective or more effective… just changing something as simple as a liquid to a tablet could actually have a big consequence" (N-106D)

Overall the majority of comments from nursing staff about taking medications were negative, reflecting multiple challenges in routine practice. In the context of a PK study these challenges could be enhanced by the need for timely and precise administration.

7.3.5.2 Facilitators to medication issues

In order to ensure the timeliness of administration of medications and accuracy of documentation staff training was felt to be important:

"...what it boils down to is education and communication I think." (N-80A)

In conjunction with this was simple, trial paperwork which prompted accuracy in documentation:

"Your prescription chart can have a little slip stapled to it that quite clearly says they are in this trial, please just write down the time you have given that drug. To the minute." (N-106C)

However, there was a recognition that with conflicting demands staff could struggle to comply with study protocols. Therefore, research staff support should also be available to help support staff with administration requirements.

7.3.6 Sampling

Participants made many comments about issues surrounding sampling for PK studies. Barriers and facilitators are summarised in *Table 46* below.

Table 46: summary of barriers and facilitators related to sampling (nurses)

	Barriers	Facilitators
Sampling	Capillary Cannulas	• Use of indwelling lines • Conduct on PIC[1]
	Blood volumes & frequency	• Guidelines • Consider alternative methods to reduce sample volume and number[2] ➢ opportunistic sampling ➢ scavenged samples ➢ population PK
	Sampling regime	• Communication with clinical teams- verbal and written • Training • Support from senior staff / research teams

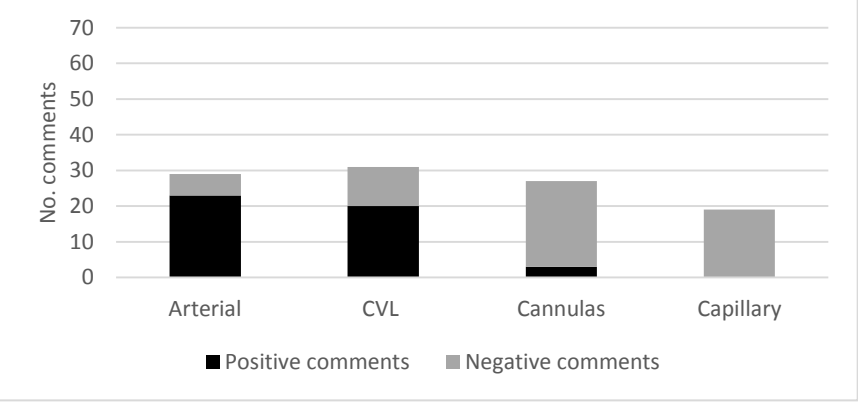
[1] See section *7.3.9*, [2]See section *7.3.4.3.3*

7.3.6.1 Barriers /challenges to sampling

7.3.6.1.1 Vascular access

All nurse participants commented on different types of vascular access in relation to sampling requirements for PK monitoring. (See *Figure 42* below for a comparison of comments).

Figure 42: views on vascular access & sampling (nurses)



Overall capillary sampling and sampling from a cannula were not regarded as reliable or pleasant methods for obtaining blood samples. All comments about capillary sampling were

negative, reflecting on the pain, distress, scarring and the time-consuming nature of this method for obtaining blood samples:

> *"I think when people come in and they have had a lot of heel pricks, their heels are...(N-61B).*
>
> *They're a mess, aren't they (N-61A).*
>
> *It looks excruciating to be fair, some of them" (N-61B) (exchange between PICU nurses N-61A&B)*

The majority of comments about obtaining samples from cannulas were also negative, relating to the pain and discomfort for CYP from the placement and manipulation. Other difficulties related to the specificity of the protocol with the location of vascular access or the achievement of required sampling volumes:

> *"And the differing limbs?... If both had to be venous cannulas, for some of our patients you don't have that luxury of being able to pick where they are placed." (N-80B)*

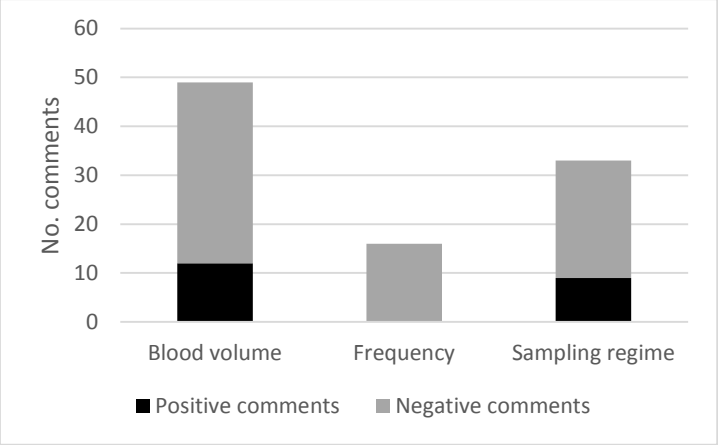
In fact, only one nurse had experience of being able to reliably obtain blood samples from a cannula that 'bled back' and this was in older CYP on an adolescent ward

> *"Well in my experiences, cannulas don't always bleed back and once you start, you might be okay for the first couple of samples but they won't stay the course and then what happens to you? You have started this pathway then what happens to the trial really, if you haven't been able to take the rest of them? Does that mean it's abandoned then?" (N-73)*

7.3.6.1.2 Obtaining samples

Three key sub-themes were discussed about obtaining samples: the blood volume a study protocol requested, the number of samples (frequency) and the specific regime or study protocol. Comments are summarised in *Figure 43* below.

Figure 43: views on study sampling requirements (nurses)



The volume of blood (16mls in total) was regarded as an issue by a number of the nurse participants. Negative comments reflected concerns about the impact of this volume for patients on PIC who were commonly under one year of age, underweight, unstable, vulnerable to anaemia and the potential need for a subsequent transfusion.

> *"And you run the risk they become anaemic because of that much sampling you are exposing them to – that's a big issue really, isn't it?" (N-61B)*

Nurses made fewer comments about the number of samples being taken, so it appeared that this was less of an issue than the overall sampled volume. However, all the comments made on this topic were negative. Staff concerns reflected the impact of extra sampling on workload as well as the enhanced infection risk for patients:

> *"In effect, you are quadrupling their infection potential... If two days down the line your patient's gone septic, you could quite reasonably say has that got something to do with it? Has that sampling regime jeopardised our patient?" (N-57F)*

There were a large number of comments about the blood sampling regime outlined within the vignette. For many the regime was felt to be too rigid, unrealistic and too difficult to achieve due to the unpredictability of the clinical environment:

"I think especially on PICU, I don't think we'd ever be able to be compliant with those time frames unless you have got a nice level one steady patient... If you have got a level four patient, you are going to really struggle to get that in." (N-57A)

7.3.6.2.3 Summary of barriers

Overall cannulas were perceived as unreliable for obtaining samples and capillary sampling was negatively viewed. Nurses were concerned about the volume of blood being sampled and the regime requirements more than the number of samples. However there were concerns about the impact of all three aspects for both the patient and the staff.

7.3.6.2 Facilitators

7.3.6.2.1 Use of indwelling, clinically indicated vascular access

Nurses commented positively about the use of arterial lines to obtain study samples, due to their ease of use, speed and reliability. Where negative comments were made these reflected concerns about increased infection risk, the potential for lines to be left in longer than was clinically required and staff having the required competency to obtain the samples:

"They can't access central lines or arterial lines without having a competency signed off for a start. So therefore, they'd have to be competent." (N-98A)

There were a similar number of positive comments about the use of CVL, again reflecting the ease of use. However, there was a slightly higher proportion of negative comments identifying that not all patients would have a CVL, the challenge of conflicting drug regimens and competing requirements for sampling:

"If it is an IV <intravenous> drug that you are giving, there is a high degree of probability, especially on ITU, that it will be given centrally. So therefore, if your protocol says that you can't sample from the same line that you gave it, then automatically you have an issue there already" (N-57A)

7.3.6.2.2 Reference to guidelines

As outlined in *7.3.4.3.3* alternative approaches which reduced the number or volume of additional blood samples were valued. However, nursing staff also felt reference to guidelines to demonstrate the safety of a study protocol was important.

7.3.6.3.3. Communication and engagement

Communication was viewed as essential throughout the conduct of a PK study to convey exactly what was required. This covered both verbal and written communication with clinical teams. Written communication in the form of simple, clear trial documentation were felt to be an important facilitating factor:

> *"As long as we knew what we were doing... we've got a tick-list... to look at, this is what we need to do when there's no one here, then I think we'd be fine" (N-99A).*

However, ultimately this was dependent on nursing staff having time to undertake the activity. Therefore, the crucial factor was felt to be support from dedicated research staff to support staff with sampling requirements.

7.3.7 Processing

Overall nurses did not recognise there to be many areas of concern related to the processing and interpretation of results from PK studies. See *Table 47* below.

Table 47: summary of barriers / facilitators in relation to processing (nurses)

	Barriers	Facilitators
Processing	Documentation accuracy	• Training • Trial related paperwork / documentation

In contrast to CYP and parents there were a number of accounts by nursing staff of issues related to the processing of PK samples in routine clinical care. Issues involved accounts of blood being put in the wrong bottles, problems with the opening times of the laboratories or issues with delays in obtaining results. One respondent summarised the situation:

"Yes, lots [of problems] [Laughter]. That's because the sample isn't taken at the right time, or put in the right vial, or sent to the right place at the right time or if they say it's gone, it hasn't arrived there. Or the results have come back late or the results haven't been phoned through or somebody's had the results and haven't conveyed it to the doctors. So, there are, lots and lots of challenges..." (N-73)

One of the issues raised about current practice was that in order for methods such as the use of scavenged samples or opportunistic sampling alongside routine bloods to work, documentation in relation to both medication administration and sampling would have to improve:

"We are notorious for the six o'clock bloods being six o'clock-ish, which is somewhere between half four and half seven, whilst still being 'the six o'clock bloods'... (N-74)

Although this topic received fewer comments than other aspects of PK research by nursing staff, staff recognised that these issues would create significant issues for a PK study. They identified that key facilitators to overcome this was training and the creation of trial-specific paperwork which prompted accuracy in documenting the sampling times.

7.3.8 Outcomes

7.3.8.1 Barriers / challenges associated with outcomes from PK research

Key barriers and facilitators are outlined in *Table 48* below.

Table 48: summary of barriers and facilitators related to study outcomes (nurses)

	Barriers	Facilitators
Outcomes	Nursing workload, prioritisation & responsibility	• Engagement with clinical teams • Support ➢ senior staff ➢ outreach research ➢ department specific team
	Lack of feedback from research	• Research is important

7.3.8.1.1 Nursing workload, prioritisation and responsibility

Throughout the discussions nursing staff referred to their workload and stated that many nurses already felt overloaded and working at capacity. If a family consented to a study they

would strive to comply with the protocol requirements, feeling a sense of personal responsibility as a 1:1 caregiver. Negative comments reflected a sense of concern that they did not want to be the person who caused a study to 'fail':

> *"...you don't want to mess everything up, especially if it is something that has been run for the last four days very well... you don't want to be the person who has then messed it up" (N-57F)*

This was counterbalanced by a recognition that although they thought research was important, their priority had to be the clinical care requirements:

> *"I have got to do what we need to do to save the child's life and then if I possibly can I'll take your samples… I did try hard to accommodate requirements for the * trial but if it had been impossible then I wouldn't have given it a second thought" (N-74)*

Staff experienced a dilemma of wanting to support research but recognising there were insufficient resources. This situation was summarised by one participant:

> *"We're willing, but not able" (N-49).*

7.3.8.1.2 Lack of feedback from research

Three nurses highlighted the frustration when the results of research were not shared with staff. One highlighted the frustration she felt when a protocol for managing a particular group of patients was amended following an RCT on the ward, but the reasons for the change was never disseminated to the nursing staff:

> *"I've got no clue what came out of it, other than the fact they <patients> are not on steroids now. From the wards point of view, that's the extent of our knowledge. They shouldn't be on steroids, that's it. As to why, I don't know… So, it's not really kind of communicated and filtered down." (N-97)*

7.3.8.2 Facilitators for successful outcome

7.3.8.2.1 Research is important

Despite all the issues identified by nursing staff, there was a general sense from many staff that research contributed to improvements in patient care. 11 staff highlighted that PK

research could lead to optimised medicines management, improve the patient journey as well as potentially reducing the length of stay:

> *"if you find that measuring drug levels, I don't know, every 8 hours or whatever, gives you a better control over the trough levels and therefore infections clear up quicker or something, then that becomes standard practice... wouldn't it?" (N-98F)*

Nursing staff wanted to understand more about the impact of research on practice, what evidence supported changes and how that information had been gained. Feedback from each study to staff was therefore identified as important.

7.3.8.2.2 Support

The biggest facilitating factor for the conduct of a PK study was support. Some nursing staff felt this could take the form of involvement of team leaders or the nurse in charge. Senior staff were identified as useful as they could provide reminders and practical support to junior staff:

> *"...if you inform the team leader or the Band 7 at least they can say at handover time, "Don't forget that this patient has to have samples done." And then they can go and try and follow it up." (N-57A)*

However, there was a recognition that support from trained research staff was the ideal method of study support, reflecting that responsibility for following the research protocol then shifted to the research staff:

> *"...if you have an independent person who is from the research team, that is purely there to take those bloods and they will turn up at that time, they'll bring whatever they need to take the bloods, they will sample independently. It means the bedside nurse can almost forget about it... Therefore, your odds of it being missed, your odds of there being a problem, are cut down because you have got that independent person". (N-57F)*

Where staff were less clear was on the place of trained research staff who were external to the department- outreach support. 17 people felt any support was valuable, however 14 people expressed concerns. These concerns reflected that external staff would not be

competent in sampling and therefore their role would be to dictate the protocol to bedside staff, without providing any practical assistance. Others reported a degree of suspicion in the competence of the research staff and would want to watch them closely to ensure they were satisfied with their technique, even when staff had evidence of training:

> *"I think we would be more suspicious, I think you'd want to watch them a couple of times... If there is some person you've never met before… they can have something signed but I'd want to see for myself" (N-61C)*

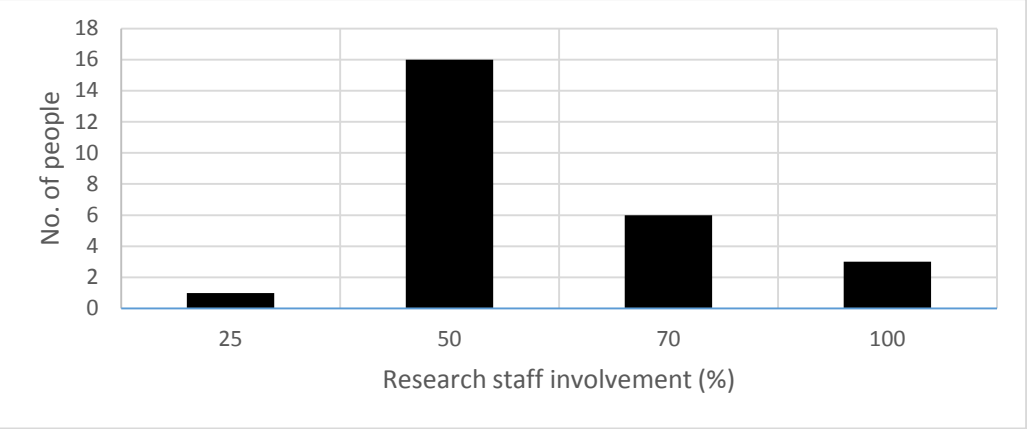
When the research team was composed of internally-trained staff, for example, a PIC specific research team, staff had far fewer concerns. They felt a PIC specific team were more familiar with the environment and could interpret the clinical situation better:

> *"Every situation I've been in where I've had a critically unwell patient and one of the PIC research team wants to talk to them, if you've said actually, I really don't think it's a good time, they've always listened... and they've walked away... I'm very conscious that you've got time limits to get these patients recruited but actually it kind of proves that their wellbeing was at the forefront of your minds as well." (N-98F).*

7.3.8.2.3 Model of support

Despite all the concerns, all 29 participants agreed that they would care for a patient in a PK study and assist with the study protocol where required (although only three nurses had actually undertaken GCP training). Where staff differed was in the level of research support they felt should be provided. Only 3 people (10%) felt research staff should undertake all study-related activity and 55% (n=16) felt a model of 50:50 shared responsibility between research and clinical staff was appropriate (see *Figure 44* below).

Figure 44: 'ideal' research nurse involvement in a PK trial (nurses views)



However, of the 55% who stated the study should be run on a 50:50 basis, 3 specifically stated this support should be split over the 24-hour period, 7 days / week with the ability to flex according to unit need which has implications for research service provision:

> *"50/50 split but you want that 50/50 split to cover the whole 24-hour period because you want to have the choice of you doing it or them doing it" (N-106D)*

Overall there appeared to be high levels of support for the conduct of PK research but this was dependent on support being available over a 24-hour period, 7 days a week which exceeds current provision.

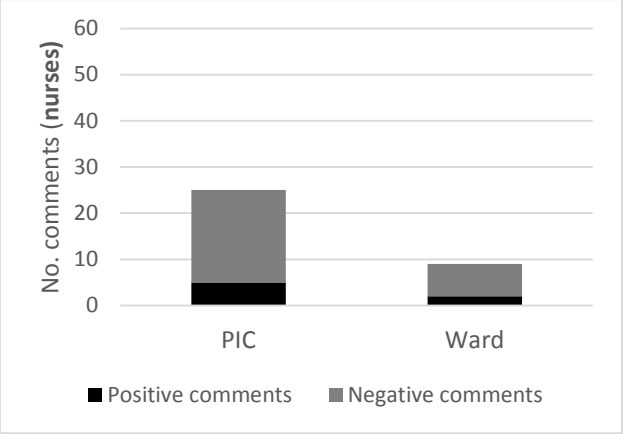
7.3.9 Context of research

A number of nursing staff expressed concerns about the conduct of PK studies in the context of inpatient wards and PIC. As none of the staff had worked within a research facility they were not asked specifically about this context. (See *Table 49* below for a summary of barriers / facilitators and *Figure 45* to show the distribution of comments).

Table 49: summary of barriers / facilitators to the context of research (nurses)

	Barriers	Facilitators
Context	PIC Wards	Support

Figure 45: the influence of context on the conduct of PK research (nurses)



In contrast to CYP and parents, nursing staff had reservations about PK research taking place on PIC. Concerns reflected the workload, the acuity of the patients and also the challenge for staff of complying with multiple study requirements:

> *"It's hard from a bedside nurse's point of view, when you're bombarded with four or five clinical trials that your patient could potentially be a part of..." (N-49)*

The ward context was also highlighted as challenging because staff to patient ratios were lower and there were issues about staff training and the lack of Registered Nurses assessed as competent to administer medications intravenously or sample blood:

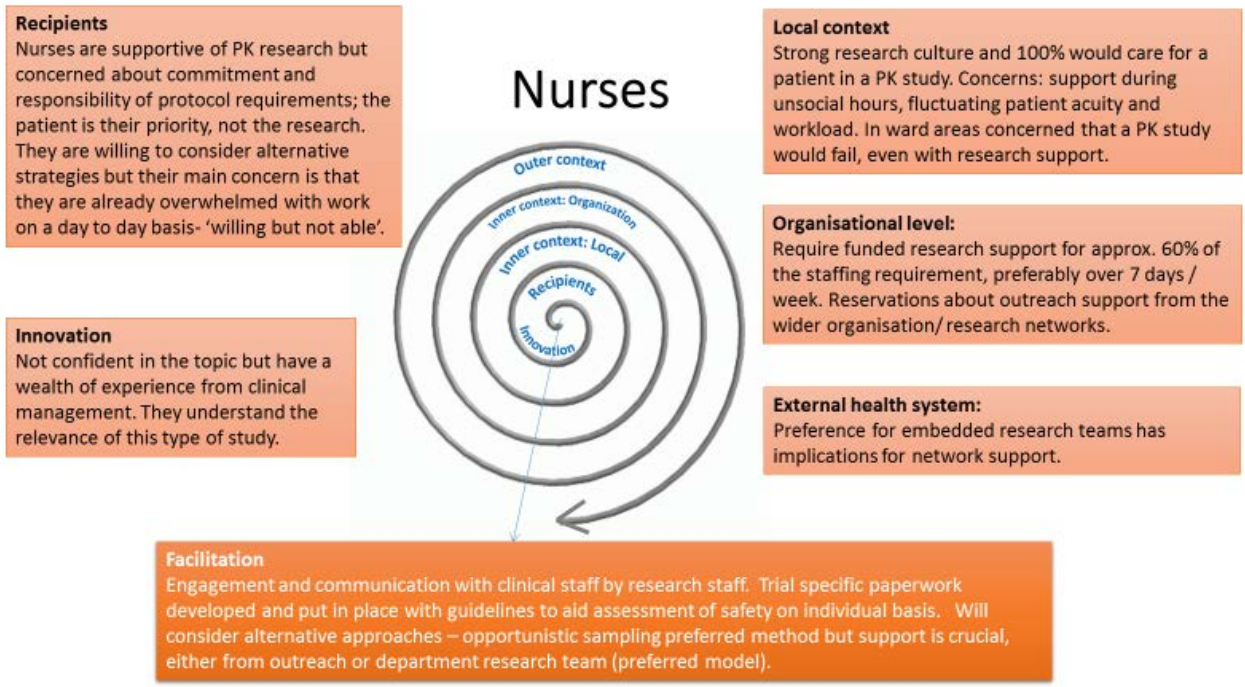
> *"I have worked on the wards… that trial would NOT work. There is no way those nurses have enough time" (N-106D)*

In summary nursing staff had concerns about all contexts, including PIC. Designated support was the only facilitator identified.

7.4 Mapping to I-PARIHS

Using the integrated PARIHS framework (Harvey and Kitson, 2016) the key aspects for the nurses as 'recipients' have been mapped out in relation to the 'innovation' – the implementation of PK research studies. Context extends from the local clinical area, to the wider organisation. See *Figure 46* below.

Figure 46: summary of nurses' responses mapped to I-PARIHS



7.5 Discussion

7.5.1 Pharmacokinetic knowledge and experience

Nurses play a pivotal role in current NHS care delivery to support and deliver evidence based practice (Department of Health, 2006). Determining research acceptability or feasibility to clinical staff is therefore fundamental if successful implementation is to occur. PRESCRIBE found that although nurses do not have experience of PK research studies, they have extensive experience from clinical management. These experiences indicate there are significant issues related to the prescription and timely administration of medications, particularly related to patient acuity, competing requirements for IV access and ward demands. These issues would be magnified in the context of a PK study and they raised concerns about the accuracy of current documentation, particularly if population PK methods of conduct were to be adopted. There are very few studies conducted exploring health care professionals' attitudes towards PK research with which to compare the findings.

A survey of attitudes towards unlicensed and off-label prescribing in paediatrics found paediatric nurses were relatively unconcerned about the safety and efficacy of unlicensed and off-label medicine use, and only 49.3% perceived there was a requirement for more clinical trials in CYP (Mukattash et al., 2011). This is consistent with a study of Paediatricians which found that although 70% had concerns about safety associated with off-label use of medicines, only 50% believed that further trials were indicated (McLay et al., 2006). These ambivalent attitudes are concerning given that medication errors are common within inpatient paediatric settings (Kaushal et al., 2001). In comparison participants within PRESCRIBE demonstrated a marked concern about the vulnerability of patients in their care and a desire for increased knowledge about the medications they utilised. This concern translated into positivity towards the conduct of PK research, with 100% of participants agreeing they would be happy to care for a child in a PK study. By contrast, only 27.7% of paediatric nurses (Mukattash et al., 2011) and 52% of Paediatricians (McLay et al., 2006) would be willing to be actively involved with a patient in a clinical research study. The reasons for these differences in attitudes are not completely apparent, but one factor that differed was that 26/29 participants in PRESCRIBE worked in Paediatric Intensive Care; an area where 70% of the medications are unlicensed or are prescribed off label (Turner et al., 1998) and multiple organ failure is common (Leteurtre et al., 2006). Nursing staff on PIC recounted experiences of feeling uncertainty in patient management in the face of liver and renal dysfunction or with the use of Extra-Corporeal Membranous Oxygenation (ECMO) and Continuous Veno-Venous Haemofiltration (CVVH). In addition, non-medical prescribing is increasing within the organisation with the result that medication management is increasingly viewed as a multi-disciplinary issue (Buckley et al., 2006). Reports from nurse

participants in PRESCRIBE therefore indicate a high level of support in principle for PK research, valuing the information for clinical management. There were concerns about the inclusion of young infants and neonates, which is of concern as approximately 50% of admissions to BCH PIC are less than one year and neonatal patients are the most exposed group to unlicensed and off label drug use (Conroy et al., 1999). Further work may therefore be required to address concerns of nursing staff about those identified as 'vulnerable'.

7.5.2 Roles and responsibility

Nursing staff were supportive of PK research and in keeping with other published literature, highlighted the importance of research for clinical practice (Nilsson et al., 1998, Bjorkstrom and Hamrin, 2001). However, they expressed concerns about the addition of extra work to an already stretched workforce, factors which have been identified in other intensive care studies (Siner et al., 2014, Browning et al., 2016). Only 20% of participants in one study felt that the practicalities of a protocol on their workload had been considered (Smith et al., 2016). The risk is that adding to the workload of clinical staff will interfere with non-research care (Alt-White and Pranulis, 2006). In recognition of this concern, nurses in PRESCRIBE were happy to share the responsibility for the conduct of the research with research staff. However, their preference was for *flexible* support, including weekend support from research staff. This would mean offering research cover seven days / week, at the very least 7.5 hours / day, ideally 12 hours / day. This level of cover is not currently available within BCH or within many (if any) tertiary children's Hospitals and would have huge implications for future resource planning and funding at the organisational level.

7.5.3 Research support

In addition to the level of support, the nursing staff within PRESCRIBE also had preferences on who provided the support. Outreach support was regarded as beneficial but overall there was a preference for support from a department specific research team who understood the clinical environment and could provide practical assistance as needed by the clinical team. Smith et al (2016) highlight that positive relationships between researchers and clinicians were associated with favourable perceptions of research and research acceptability amongst nurses. Indeed 81% of nurses who had cared for a patient in a multi-centre PICU study agreed that they felt part of the trial team (Browning et al., 2016). Whilst the significance of good working relationships is highlighted by the published literature, there is little reference to who provides this research support or preferences on the provision. What is known is that there needs to be significant investment of support prior to the commencement of a study (Smith et al., 2016), good communication about the ongoing progress of a study (Alt-White and Pranulis, 2006) and also feedback about the results (Kahn, 2009). These were all recognised by nurses within PRESCRIBE. It is conceivable that good working relationship are more likely to happen when research staff are embedded within a unit. Within the last ten years, however, there has been a move towards research nurse support from NIHR Research Networks (National Institute for Health Research, 2016b). These resources are often not department specific and therefore staff may not be familiar with, or competent, within an environment such as PIC

7.5.4 Research culture

All 29 nursing participants were supportive of caring for future patients in PK studies, despite practical concerns about the impact on their workload. This positivity towards research is suggested to develop when nurses work in research-active clinical areas (Hek and Shaw,

2006). This is supported by Browning et al (2016) who report that nurses with at least 3 years PIC experience were more likely to have positive perceptions of a trial they were supporting (THAPCA) than those with less experience. Perceptions were also more positive for nurses who had cared for a patient in *any* research study versus those who had not. In Smith et al (2016) 63% of participants had cared for patients in a research study over 5 times in the previous 12 months and 78% reported that research leads to improved care. The literature therefore seems to suggest that exposure and experience of research increase positive attitudes towards research. This is supported by findings from PRESCRIBE, where many of the nurse participants (both PIC and non-PIC nurses) had experience of caring for patients in research studies. Even when there were significant concerns about their workload, staff still felt PK research was important. However, when the context of the vignette moved to ward areas, staff became less supportive, even with the presence of outreach support. Positivity therefore appears to be dependent on the local culture and practical support availability.

7.6 Limitations

With the majority of respondents working on PIC, the results are heavily oriented to the perspective of PIC. The study protocol had specified recruitment through ward managers so when Ward Managers failed to respond, there were limited opportunities to recruit clinical nurses from ward areas. A future recruitment strategy would be wise to utilise multiple recruitment strategies to ensure recruitment is not limited by gatekeepers. PRESCRIBE was focused on the issues surrounding the conduct of PK studies in critically ill children therefore the perspective of PIC nurses was the most important.

Nurses were not asked about whether they themselves were parents. Three nurses did make reference to personal experiences of administering medications or their child requiring blood samples. Overall staff focused on their professional, rather than personal experiences so this did not appear to be a significant influence on staff attitude.

In a dynamic environment such as PIC which also experiences rapid staff turnover there is the possibility that staff attitudes have changed since the interviews were conducted in 2013/14. A national report of PIC activity indicates that the acuity of PIC patients is increasing and many units are struggling to meet the recommended staffing levels (PICANet, 2016). It would therefore seem that staff concerns about workload and ability to support research activity are likely to remain valid.

7.7 How does this qualitative work with nurses address the knowledge gap surrounding pharmacokinetic studies?

This chapter set out to address gaps in knowledge associated with the health care professional perspective, specifically the perspective of nurses, the influence of context and facilitation and has addressed all three aspects.

1. Health care professionals can play a pivotal role in influencing the success implementation of interventions or results from research (Thompson, 2012, Rycroft-Malone et al., 2013). However, there are very few papers exploring the attitudes of nursing staff towards research. Only one published account of PK research within the PICU context was identified and this emphasised the challenging nature of this environment, particularly ensuring the accuracy of timing (Siner et al., 2014). However, this study was in abstract form only and the method of study was unclear so limited conclusions can be drawn. PRESCRIBE is the first study the researcher is aware of to explore attitudes of clinical nurses towards PK research

studies in the context of PICU. Findings suggest that Paediatric Nurses are supportive of PK research but there are a number of barriers which need to be addressed in relation to the timely administration of medications, sampling and overall compliance with a study protocol.

2. The influence of context on research conduct and staff attitudes is also an area where little research has been conducted. Existing literature is also limited by the inclusion of participants from both PIC and Adult Intensive Care settings (Smith et al., 2016) and by the use of surveys, which limit further exploration of attitudes (Smith et al., 2016, Browning et al., 2016). PRESCRIBE is one of only a few studies to explore PIC nurses' attitudes specifically, using interactive methods and explore the influence of context on research conduct. The findings provide evidence that nurses support the idea of PK research taking place in PIC but have serious concerns about the conduct within a ward area. This is an important message for those funding, designing and approving the conduct of PK studies.

3. The third gap in the knowledge this work addresses is the identification of facilitators for future study design and conduct. Nurses value strategies that demonstrate safety for patients in their care, good communication between clinical and research teams as well as support from research personnel. Findings suggest that there is a discrepancy between staff preferences and current research provision, which may hinder future research conduct.

7.8 Conclusion

Although the term 'pharmacokinetics' was not necessarily one nurses were familiar with, they had a working understanding of the significance and could see the value of increased information for medicine management. The nurse stakeholder group prided themselves on

prioritising the care of patients and their families and they had a strong sense of responsibility for patients in their care. They were supportive of PK research overall but collectively they agreed that they would struggle significantly to adhere to a protocol such as the one in the vignette. Facilitation was predominantly about having dedicated research support- ideally from a PIC specific research team who could work flexibly, dependent on unit needs. The current NHS research infrastructure is often from generic teams of research personnel; however, this is not in line with clinical nurses' preferences. Funders and researchers must seek to address these concerns or risk alienating and losing the support of clinical staff and compromising the quality of research studies.

Chapter 8: Exploring the attitudes of research personnel towards Pharmacokinetics studies in critically ill children

8.1 Introduction

8.1.1 What is known about research personnel attitudes toward PK research?

Setting up and running a clinical trial is a complex process that takes time, planning and resources (Pick et al., 2011). Whilst a variety of personnel are required to assist with the delivery and support of research (Tattersall, 2002, National Institute for Health Research, 2016c) much of the day to day management is undertaken by Clinical Research Nurses (CRN) (Mori et al., 2007, Pick et al., 2011, National Institute for Health Research, 2016d). The role is not exclusively the domain of nurses and there are a variety of other terms used within the published literature including Clinical Research Associate (Grunfeld et al., 2002, Tattersall, 2002, Wright et al., 2002), Research Assistants (Cambron and Evans, 2003), Research Associates (Ulrich et al., 2010), and Clinical Research Coordinators (Rico-Villademoros et al., 2004). However, whilst the title and clinical background have varied in different settings what is consistent is the importance of a role in enrolling and following patients throughout the clinical trial process. For the purposes of continuity and clarity henceforth the role is referred to as Clinical Research Nurse (CRN). The role of the CRN is vital and the most common skills and responsibilities include screening, recruitment and obtaining informed consent from patients and/or relatives; administration of the intervention being studied; monitoring participants, collecting data and reporting any adverse events (Connolly et al., 2004, Mori et al., 2007, Gibbs and Lowton, 2012). In fact once a trial has been successfully

approved Principal Investigators have been described as having a relatively 'hands-off role', with research work only constituting about 5% of their workload (Lawton et al., 2012). The CRN with their key responsibilities for recruitment and involvement in trial implementation has a pivotal role for successful trial conduct (Connolly et al., 2004, Gibbs and Lowton, 2012, Lawton et al., 2012). This highlights the value of understanding the experiences of the CRN, particularly in relation to recruitment. A meta-synthesis of researchers and clinician's perceptions of recruiting participants to clinical research was recently conducted (18 papers included) (Newington and Metcalfe, 2014). However studies discussing the recruitment of patients unable to give informed consent, such as children and young people (CYP) and studies in intensive care setting were specifically excluded due to the additional ethical issues surrounding these populations. One of the key findings from the meta-synthesis was that compromise was required to create study designs that were acceptable to all involved. Understanding the perspectives of all concerned in trial conduct is therefore invaluable (Tinkler et al., 2018). Further research is warranted to ensure the experiences of those conducting research with populations such as CYP and in contexts such as intensive care is captured as this is missing from the current evidence-base.

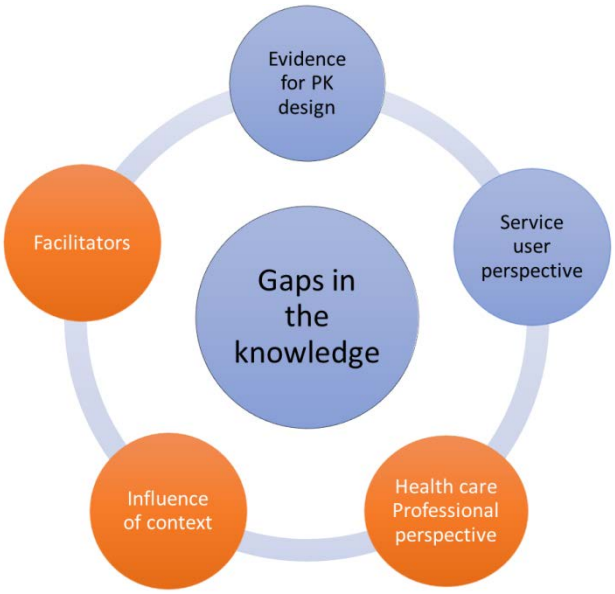
8.1.2 What is known about the approvals process for pharmacokinetic studies?

In addition to permission from Research Ethics Committee (REC) approval to conduct research within the NHS, researchers must also have confirmation of management permission from each local site (National Institute for Health Research, 2016e). A parliamentary report on clinical trials highlighted that separate local NHS Research and Development (R&D) approvals was one of the biggest barriers to initiating clinical trials in the UK and contributed to a 22% decline in the number of clinical trials conducted in the UK

between 2007 and 2011 (House of Commons Science and Technology Committee, 2013). The time taken for local R&D departments to approve the application has been the primary focus of criticism (Elwyn et al., 2005, Al-Shahi Salman et al., 2007, Hackshaw et al., 2008, Mallick and O'Callagan, 2009), often with no explanation for delays (Al-Shahi Salman et al., 2007, Hackshaw et al., 2008). There are suggestions that REC members can have concerns about the conduct of research with CYP, particularly where there are additional invasive procedures (Angell et al., 2010). However, little is known about the considerations R&D departments make when reviewing a research protocol or about their decision-making priorities. Further research is required to understand more about the attitudes of R&D departments, particularly given the serious impact of delays on successful study conduct.

Chapter 8 aims to address the gaps in knowledge related to research staff attitudes towards PK research, explore the influence of context on research staff attitudes and identify facilitators to research conduct (see *Figure 47* below).

Figure 47: gaps in the knowledge- research personnel



8.2 Research aims

The aim of this work was to determine the attitudes of research staff (Clinical Research Nurses (CRN) and Research and Development (R&D) panel members) towards paediatric PK studies, identify what participants perceived to be a barrier or problematic about the conduct of paediatric PK research studies and identify what participants identified as enabling or facilitating the conduct of PK research studies. Please see Chapter 2 for full details of the methods undertaken.

8.3 Results

8.3.1 Demographics

Recruitment to focus groups and interviews took place between 01.04.2013 and 01.04.2014. 47 Research staff participated in nine focus groups (FG) (n=42) and five interviews (n=5). One focus group (with 4 CRN West Midlands staff) was of too poor audio quality to be analysed, therefore, results from 43 research staff (8 FG and 5 interviews) are reported.

- Ward specific (Birmingham Children's Hospital (BCH))– Paediatric Intensive Care (PIC) (n=5) & Burns ward (n=1) = 6
- Wellcome Trust Clinical Research Facility (WTCRF) (BCH): 13
- Neonatal research team (Birmingham Women's Hospital (BWH)): 3
- National Institute Health Research (NIHR) Research Network (West Midlands (WM)): 8
- National Institute Health Research (NIHR) Research Network (South West (SW)): 13

Participants included Band 5 (n=5), Band 6 (n=33), Band 7 (n=5) (see *Table 50* below). *Table 51* provides the codes for participants' ages, paediatric experience and research experience. Despite person specifications within the NIHR Research Network posts being open to Allied Health Professionals, all staff were Registered Nurses. The term Clinical Research Nurse (CRN) is therefore utilised. CRN staff worked in a variety of areas and hospitals.

Table 50: recruited CRN staff participants' demographics

Participant	Age	Gender	Band	Department	Paeds experience	Research experience	Method
45A*	2	F	6	PIC	3	2	FG 1
45B*	3	F	6	PIC	4	2	FG 1
45C*	3	F	6	PIC	3	2	FG 1
45D*	4	M	5	PIC	3	2	FG 1
45E*	5	F	6	PIC	5	3	FG 1
48*	4	F	6	NIHR (WM)	5	3	Interview
50A*	3	F	6	WTCRF	3	1	FG 2
50B*	5	F	6	WTCRF	5	1	FG 2
50C*	3	F	6	WTCRF	4	1	FG 2
52A*	3	F	6	NIHR (WM)	4	1	FG 3
52B*	5	F	7	NIHR (WM)	1	4	FG 3
52C*	5	F	7	NIHR (WM)	5	2	FG 3
52D*	5	F	6	NIHR (WM)	5	2	FG 3
52E*	5	F	6	NIHR (WM)	5	3	FG 3
52F*	4	F	6	NIHR (WM)	5	3	FG 3
52G*	5	F	6	NIHR (WM)	5	3	FG 3
67*	3	F	6	WTCRF	3	1	Interview
68A*	2	F	5	WTCRF	2	1	FG 4
68B*	1	F	5	WTCRF	1	1	FG 4
68C*	1	F	5	WTCRF	1	1	FG 4
72A*	5	F	6	WTCRF	5	1	FG 5
72B*	2	F	5	WTCRF	2	1	FG 5
72C*	3	F	7	WTCRF	4	3	FG 5
72D*	3	F	6	WTCRF	4	3	FG 5
77*	2	F	6	WTCRF	3	3	Interview
78*	3	F	6	WTCRF	3	2	Interview
79A*	3	F	6	Neonatal	4	3	FG 6
79B*	5	F	6	Neonatal	5	2	FG 6
79C*	5	F	6	Neonatal	5	2	FG 6
88A*	5	F	6	NIHR (SW)	5	2	FG 7
88B*	4	F	6	NIHR (SW)	5	3	FG 7
88C*	2	F	6	NIHR (SW)	3	2	FG 7
88D*	2	F	6	NIHR (SW)	3	1	FG 7
88E*	5	F	7	NIHR (SW)	5	3	FG 7
88F*	5	F	7	NIHR (SW)	5	3	FG 7
88G*	3	F	6	NIHR (SW)	4	3	FG 7
88H*	5	F	6	NIHR (SW)	5	3	FG 7
88I*	4	F	6	NIHR (SW)	5	3	FG 7
94*	4	F	6	Burns	4	2	Interview
95A*	4	F	6	NIHR (SW)	5	2	FG 8

Participant	Age	Gender	Band	Department	Paeds experience	Research experience	Method
95B*	3	F	6	NIHR (SW)	4	2	FG 8
95C*	4	F	6	NIHR (SW)	5	2	FG 8
95D*	5	F	6	NIHR (SW)	5	1	FG 8

*= GCP trained

Table 51: codes for age and experience of CRN participants

Code: Age	Experience
1= 21-24 years	1= </=2 yrs
2= 25-29 years	2= >2 years- 4.9 9yrs
3= 30-35years	3= 5- 9.99yrs
4= 36-40years	4= 10- 14.99 yrs
5= 41-50 years	5= >/=15 yrs

R&D participants included R&D Manager, representative from laboratories, a trials portfolio manager and Research administrator (see *Table 52* below) (4/10 panel members).

Table 52: summary of recruited R&D participants' demographics

Participant	Age	Gender	Band	Department	Paeds experience	Research experience	Method
118*	3	F	8C	R&D[1]	3	4	Interview
119A*	5	M	8A	R&D[2]	5	4	FG 1
119B*	4	F	6	R&D[3]	3	3	FG 1
119C*	5	F	6	R&D[4]	5	5	FG 1

[1]R&D manager, [2]Laboratory Research Manager, [3]Trial portfolio manager, [4]Research administrator *= GCP trained

Following introductory material all CRN and R&D staff stated they felt comfortable with the topic of pharmacokinetics. When questioned for a definition, some provided a relatively detailed response, reflecting an understanding of what a PK trial would incorporate:

> *"pharmacokinetics is what the body does to a drug as opposed to pharmacodynamics, which is what the drug does to the body. Obviously, it involves a child taking a drug, whether it be orally or an injection or intravenous, and then monitoring at set points, taking a sample of blood to see how the body's metabolising the blood, toxicity levels, things like that, and it can be blood or urine as well" (CRN-48)*

Other comments reflected a more practical, outcome-focused definition associated with getting the dose 'correct' for patients. 27/43 (63%) had experience of caring for a patient in a PK research study, particularly those working within the WTCRF (11/13).

8.3.2 Themes

Coding was condensed to the six core themes referred to within chapter 6. Quotes from CRN and R&D staff are cited as CRN- or RD- followed by their individual study number.

8.3.3 Attitudes of research personnnel

8.3.3.1 Attitudes of CRN

CRN made large numbers of comments about the positive and negative aspects to conducting PK research (see *Table 53* below).

Table 53: summary attitudes towards PK research (CRN staff)

Positive comments (56%)	Negative comments (46%)
• Inclusive approach • Families value choice & opportunity • Enhanced understanding of health condition for family • Age of CYP	• Vulnerability • Health status • Burden on families • Influence of past experiences • Experimentation • Communication and comprehension difficulties • Age of CYP • Impact on staff

CRN staff appeared to think positively about PK research with all CYP, but particularly in populations with rare diseases where there were limited treatment opportunities. There was a feeling that research provided these families with some choices and the opportunity to gain knowledge and information about their child's disease.

> *"I think there's an element of as a research nurse... we're in danger of thinking we know best. And so, we might not ask a family or we might not let them know what's going on so as not to trouble them... But if you have a child with a chronic illness, even if you can't take part in a study, you like to know what's going on. You like to know what may be out there in the future." (CRN-88E)*

Negative comments reflected the challenges of approaching and conducting this type of research, with particular emphasis on the perceived vulnerability of the child, the distress of both the CYP and parents, the influence of the child's health status, the burden of study requirements, the concept of experimentation and the challenge of communicating effectively with CYP and parents with comprehension and communication difficulties. Age of the CYP was identified as both a positive and negative influence, reflecting the challenges associated with conducting research in both older and younger CYP. Staff made numerous references to how they felt parents and CYP would feel about participation in PK research. CRN attitudes therefore appeared to be heavily influenced by the risks: benefit assessment they felt CYP and parents would conduct, although there was also some recognition of the challenges of conducting PK research for staff. Overall CRN staff demonstrated a positive attitude towards PK research, with 100% (of those asked) supportive to working on a PK study (see section *8.3.8.2.6*).

8.3.3.2 Attitudes of R&D staff

Although R&D staff reported some of the same positive impacts of participation within PK studies as CRN staff, generally their attitude was more circumspect. They focused predominantly on the practicalities of service provision (see *Table 54* below) and were less concerned about what a study involved. This slightly indifferent attitude appeared to reflect the huge influence of organisational prioritisation.

Table 54: summary of staff attitudes towards PK research (R&D staff)

Positive comments (35%)	Negative comments (65%)
• Families value choice & opportunity • Enhanced understanding of health condition for family	• Vulnerability • Health status • Impact on service provision

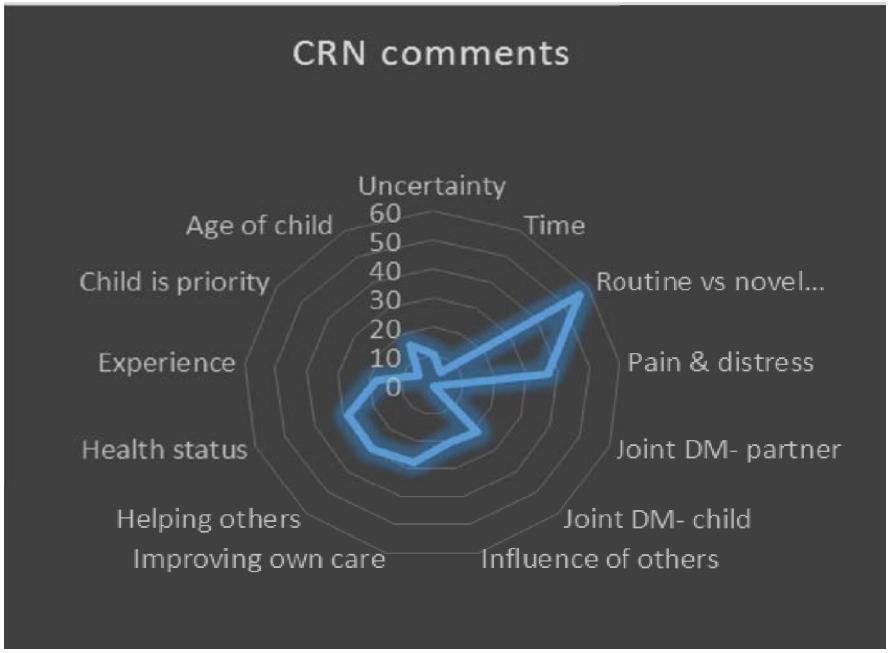
8.3.4 Recruitment

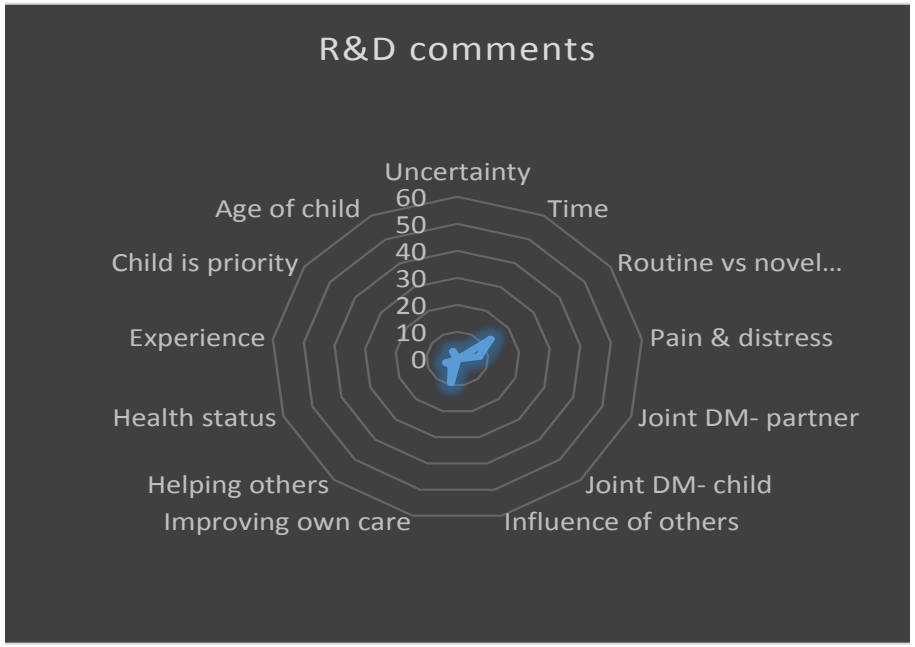
Similar to the accounts by CYP and parents, recruitment was by far the most discussed aspect of PK research conduct amongst R&D staff and the second most discussed area by CRN staff. Within this sub-theme many discussions focused on factors influencing the decision-making process.

8.3.4.1 Research staff perspectives on parents' decision making

Overall there was congruence between CRN and R&D staff on the five most commented on factors (see *Figure 48* below). These included routine vs novel treatments, improving their own care, pain and distress, health status and helping others. Where the two groups differed was that R&D staff identified less influential factors and made far fewer comments about parent decision-making. Instead they focused more on factors that influenced their decision-making (see *8.3.4.2).*

Figure 48: number and distribution of comments made by CRN and R&D staff about parental decision-making





1. Routine vs novel treatments

Both groups of research personnel felt the type of study was one of the biggest influences on a family's decision-making. This was the most commented on aspect by both sets of participants. If the drug was novel, not normally available or there were few treatment options available families would be open to considering recruitment. In fact, there were anecdotes of research staff being contacted by families internationally trying to access clinical trials and tales of families feeling torn when their chid wasn't 'sick enough' to participate:

> *"my colleague... received emails from India and all over the world, families who'd got her contact from websites and things, desperate to come on the trial. And that was hard to deal with, really, because you knew how desperate they were, we just had to pass them on to the consultant, really, and he'd have to explain that not everybody can be on it..." (CRN-48)*

If the trial was for a 'routine treatment' or where there was no direct benefit to the CYP, staff felt recruitment could be more challenging.

2. Pain and distress

Both sets of participants recognised that additional painful procedures for research purposes were likely to negatively influence decision making by CYP and parents:

> *"Even from being a patient yourself, you don't want to have extra stuff stuck in you if you don't need them or extra injections if you don't need it. That's from an adult's perspective, let alone a child's where it's going to be difficult to get veins and would cause undue distress." (RD-119B)*

CRN staff provided numerous examples of the impact that painful procedures had and felt that many CYP did decline participation due to extra invasive and painful procedures:

> *"Oh yeah. I've had children not take part in a study because of the possibility of having bloods done. They're happy to have everything else done but they don't want bloods taken. So, they can't carry on with the study because of that." (CRN-72A)*

3. Health status

Both sets of participants felt parents' decision making would be influenced by their child's condition at the time of being approached. Comments reflected parent's struggle to make decisions in the face of an emergency or life-threatening episode and an admission to PIC:

> *"If they are in for something more major, I don't know, like meningitis or something, yes I think that it would be low down as a parent on your list of priorities to agree to doing something like that." (CRN-95C)*

4. Help others

The motivation to help others was referred to by 19 CRN staff. CRN staff felt there was a high level of altruistic feeling towards research which might benefit other people in the future amongst CYP and parents, particularly amongst those with life-limiting conditions:

> *"...They may be aware that they have a limited life span but they still want to comply with some research and give something back…They just remember what it was like at the beginning for them and so they want to give something back." (CRN-88C)*

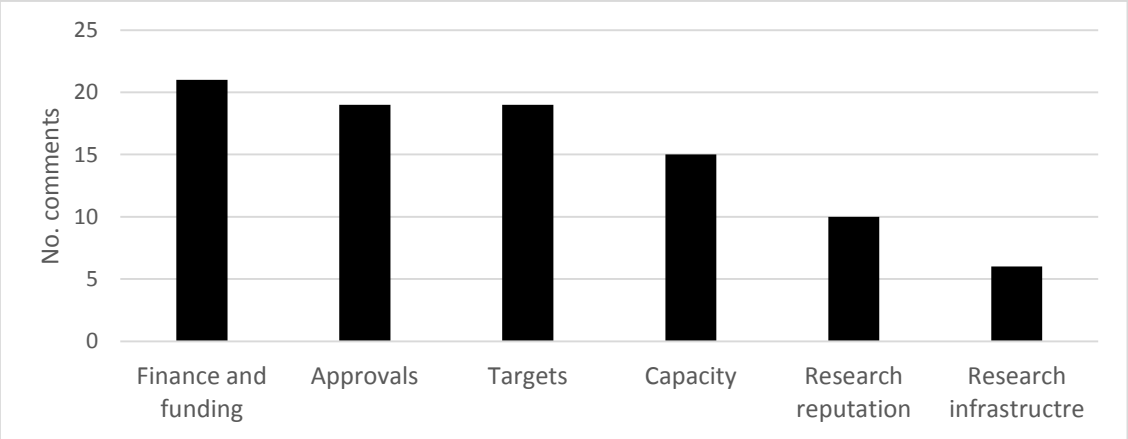
Altruism as a motivator however was rarely mentioned by R&D staff, with only one of the interviewees making reference to it.

In summary although the most commented on aspects of decision-making were similar between CRN and R&D staff, R&D staff focused on CYP and parents participating to improve or access treatments for their own benefit. Although CRN staff did show some congruence with those of CYP and parents (reported in chapter 6) their prioritisation differed.

8.3.4.2 R&D staff decision-making

In addition to discussing influences on CYP and parents' decision making, R&D staff also discussed factors that influenced *their* decision making about research approval. Comments focused on finance and funding, approvals, targets and capacity (see *Figure 49* below).

Figure 49: decision making priorities of R&D staff



Hospitals have experienced drastic financial cuts from the Department of Health for research activity and this manifested in staff focus on funding availability as the most important metric in decision-making:

> *"...our funding has been cut substantially over the last few years, we've gone from about one-and-half million down to about 600,000, that's had a massive impact… It won't get approved if it hasn't got funding associated with it." (RD-118)*

Staff were also critical of the approval process by Research Ethics Committees (RECs), with comments reflecting a lack of scrutiny of research of paediatric trials. The result was they felt studies were approved which placed excessive burden upon CYP and their families:

> *"They seem to be approved almost too easily sometimes, particularly where there is a young age group and... they're asking for a lot of blood from a very young child, but approval never seems to be a problem… once demands have been approved by Ethics Committees, it's quite difficult for us to say, "Well actually, we don't agree with that." (RD-119A)*

As well as finding it challenging to contest REC approved protocols the R&D panel also found it challenging to question the internal approvals process. The team cited cases of researchers with numerous studies in a department with limited resources approving more studies. They were therefore concerned about capacity and felt a sense of powerlessness to request changes or to refuse a study if there were concerns:

> *"We ask for the clinical lead's approval and if the clinical lead says yes then we assume, rightly or wrongly, that they are aware of this study and they know the implications for their department. We can't make that judgment that's why we have to ask them. So, we have to trust them when they say, "Oh yes, we can do this study." (RD-119C).*

All four members of staff reported concerns the hospital had reached research capacity. Targets were therefore referred to and there was a clear dilemma about approving studies where targets were not achievable and a study could therefore be perceived to be 'failing'.

CRN staff did allude to recruitment targets but were less driven by these as a metric. R&D Committee members were most concerned about a study having sufficient funding and having been costed appropriately rather than the specifics of what a study involved.

8.3.4.3 Barriers to recruitment

The biggest barriers to decision-making about PK study participation R&D staff perceived to be studies with no personal benefit / no novel treatments, pain and distress and the health status of the CYP at the time of approach. Other barriers / issues were identified during discussions surrounding recruitment (see *Table 55* below for a summary of barriers and facilitators).

Table 55: summary of barriers / facilitators to recruitment (CRN & R&D staff)

	Barriers	Facilitators
Recruitment	Infants Palliative patients	• Personal benefit to research • Choice / opportunity • Helping others • Patient and Public Involvement (R&D)
	Severity of health status	Deferred consent[1]
	Pain / distress	• Analgesia • Use of indwelling lines for sampling[2]
	Experimentation	Access to novel treatments
	'Routine' medication	• Personal benefit • Help others
	Past experiences	• Engagement with clinical teams[3] • Communication • 'The approach'
	Lack of choice	Access to novel treatments
	Extra hospital appts	• Planning • Piggy-backed to clinical appts
	Missing school	• Home visits • Overnight stay
	Travel	
	Funding	Approval procedure review
	Capacity	CRN review
	Targets	• Realistic targets set • CRN review

[1]See section *8.3.4.4.7* [2]See section *8.3.6.2.1* [3]See also *8.3.8.2.2*

8.3.4.3.1. Study subjects

CRN staff worked in a variety of environments and with a variety of patient groups. Despite these differences CRN staff were united in the need to be inclusive to approaching patients and their families:

"I think everybody deserves the opportunity to be offered the research... I don't think a certain patient group should be denied something or you make the decision that they shouldn't be included" (CRN-95C)

By comparison R&D staff made far fewer comments on this subject (see *Figure 50* and *Figure 51* below).

Figure 50: vulnerable study participants (CRN staff comments)

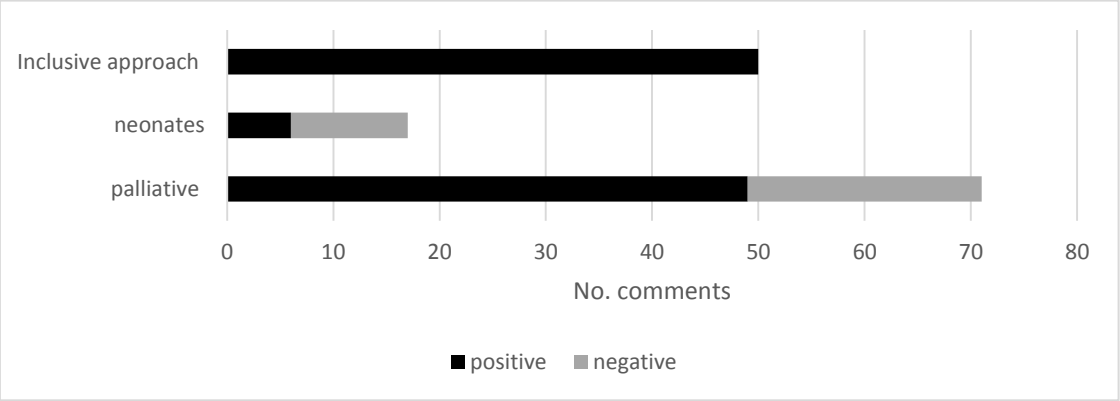
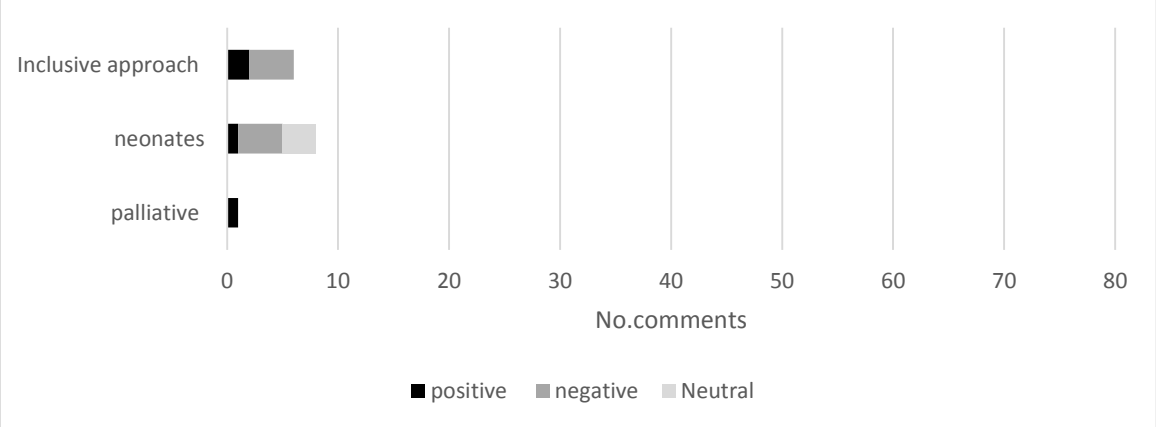


Figure 51: vulnerable study participants (R&D staff comments)



Both groups of participants became more negative in their comments when inclusion in research extended to infants, although only two people (CRN staff) specifically stated to exclude them:

*"Our parents **struggle,** struggle so much to take in what has happened to them. Even if they were expecting it, they still struggle to take in what has happened" (CRN-79A, research staff on NICU)*

There were some reservations about approaching families of a CYP on a palliative pathway by CRN staff, although the right of families to choose was recognised. Some staff made comparisons between the right to choose about research participation and the organ donation movement:

> *"It always puts me in mind of organ donation – that sort of scenario does – and there's lots of evidence in organ donation that supports the fact that the families were glad to have been given that choice" (CRN-45A)*

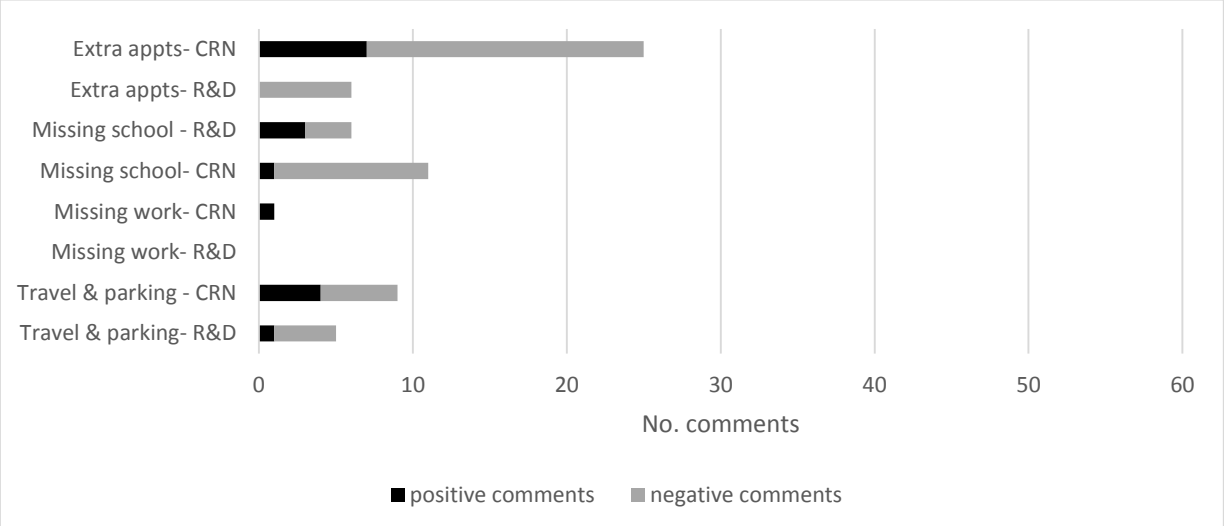
There was also a recognition that palliative patients were not necessarily 'dying' immediately and research could also lead to optimisation in their care, such as in pain management.

> *"And the drugs that they might be taking... Morphine, for comfort – are they receiving enough?" (CRN-45D)*

8.3.4.3.2 Hospital appointments

The subject of appointments specifically for research yielded a high number of comments from CRN staff on some aspects (see *Figure 52* below).

Figure 52: the impact of research appointments (CRN & R&D staff views)



Extra hospital visits were raised as a concern for families considering participation by both CRN staff and R&D staff, as these were often in addition to clinically required visits. There were concerns this could affect recruitment:

> *"Even if they've come into the hospital on a monthly basis, which is fairly frequent, studies that ask them to come every week for medicine, to them that's too much. We're had studies not recruit because of that." (CRN-72D)*

Missing school was also recognised as an influential factor by 7 CRN Staff:

> *"...school actually, is the big thing. It's not so much parents work. I find a lot of them saying they already miss enough school as it is, so that's the big one. So that can be a problem, when they're having to take additional time off school..." (CRN-48)*

In comparison this was only referred to by one participant from the R&D staff. Both CRN and R&D staff recognised that travel might impact on decision-making by families, particularly as many patients already travelled significant distances for their care provision:

> *"...they tend to drop out. And a lot of the reasons is because of the blood samples or they don't want to travel back to the hospital. That's been some of the reasons, because they have to travel." (CRN-94)*

However, in comparison to comments by parents in chapter 6, neither group recognised the extent of this as an influential factor.

8.3.4.3.3 Summary: barriers to recruitment

In summary, there were many issues surrounding recruitment to PK research for CRN staff. Decision-making was felt to be negatively influenced by a lack of personal benefit, the potential for pain and distress and the requirement to make decisions at a time of deteriorating health status. Although there were concerns about the approach of vulnerable populations, staff supported the concept of broad inclusion criteria. Additional hospital appointments were viewed as problematic, particularly because of the potential for CYP to miss school. R&D staff were less focused on who and what the study involved and more

about unrealistic recruitment targets, the capacity of the department to support the study and the funding available.

8.3.4.4 Facilitators to recruitment

8.3.4.4.1 Having a choice

Many CRN staff felt families valued having a choice and the opportunity to contribute to future health care as well as the potential for personal benefit, such as improved pain management. There were also comparisons to that of the organ donation movement; recognising that being approached about research could become more acceptable over time.

8.3.4.4.2 Emphasise the benefit of personal participation

Personal benefit was perceived to be the biggest influence for families on the decision to participate. Studies that offered access to novel treatments were felt to be a positive influence as they offered access to treatments not widely available. For more 'routine' medication there was a recognition that these could be more difficult to recruit to. Both CRN and R&D staff therefore highlighted the importance of offering some form of personal benefit or enhanced level of care or monitoring for the child from participation:

> *"a lot of the families we have in the study are from quite specialist areas and very up on the knowledge of their disease... and they take part when they realise there is a benefit to them" (CRN-95A)*

8.3.4.4.3 Communication and 'the approach'

The importance of getting the level and depth of communication with parents and with clinical staff was referred to by CRN personnel. There was also reference to the importance of the initial approach and contact with families about a PK research study. Key factors from the CRN perspective were sensitivity, timing and an ability to assess each individual situation

and circumstance. There was also reference to the personal qualities of the individual carrying out the approach:

> *"It's one of those on-the-job things, isn't it? Because you kind of learn how to manage it and I suppose get more confidence on the difficult conversations and not 'comfortable', but more able and confident to do it." (CRN-95C)*

This congruence with CYP and parents indicates that both potential participants and research staff are aware of the importance of this early contact to facilitate the recruitment process.

8.3.4.4.4 Reassurance of safety

Similar to service users and nurses, research personnel recognised the importance of safety as an influential factor on recruitment and study retention. Key components to reassure patients and staff about safety were good working relationships with clinical staff, reference to guidelines (see *section 8.3.6.2.2*) and the provision of training. Education for clinical staff helped them to understand their roles and responsibilities and how to troubleshoot, which was vital when there was no research cover:

> *"I did a similar study in <adult> intensive care… I mean, you can imagine how many nurses you'd need to train up because any one of those nurses could have ended up nursing one of these patients... I can't say that everything went completely smoothly…. It was just a matter of being available to support those staff who had not done research before and mitigating for all those things that might go wrong" (CRN-52B)*

8.3.4.4.5 Analgesia and distraction techniques

The pain and distress that painful procedures could cause were recognised by CRN and R&D staff to influence CYP and parents' decision-making. The use of topical analgesia and the use of distraction therapy were therefore identified as potential facilitators, although neither were regularly specified within a study protocol:

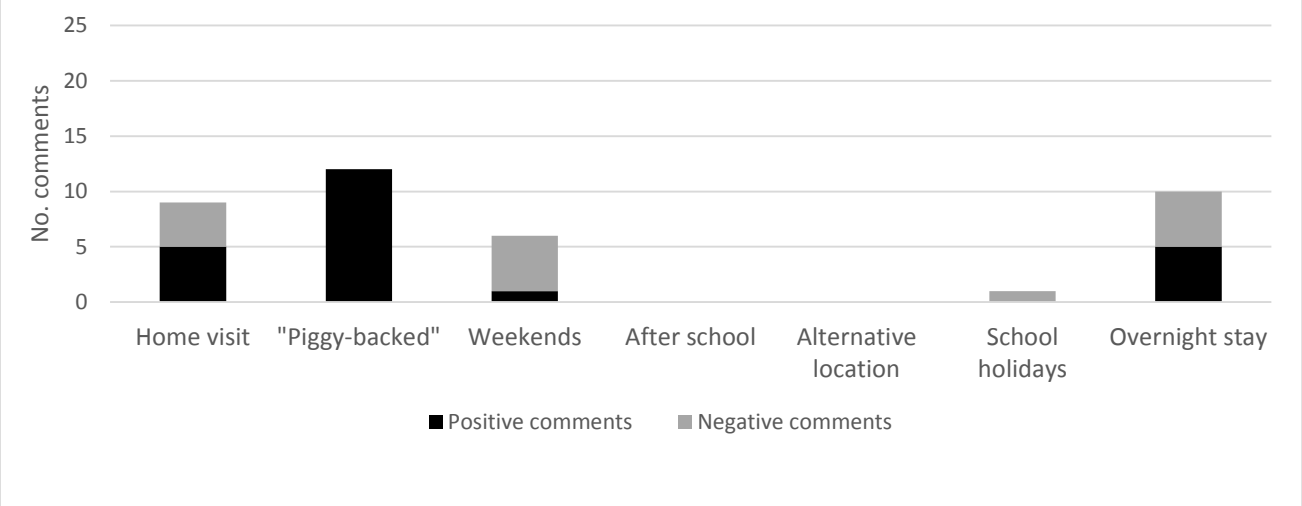
> *"It's just down to things like applying an anaesthetic cream prior to sampling, that's not always in the protocol. I don't know. I just feel sometimes it's written as, you can just do it there and then (clicks fingers), when you can't. We're dealing with children, not adults." (CRN-78)*

However, for the scale of the problem there were relatively few facilitators identified by CRN staff and none from R&D staff.

8.3.4.4.6 Avoid / combine research appointments

Extra hospital visits and missing school were identified as barriers for families considering participation in PK research studies. Different methods to reduce the impact of these were discussed, see *Figure 53* below.

Figure 53: alternative approaches to research appointments (CRN staff)



The top three methods are summarised in *Table 56*, although overall there were relatively few facilitators identified by CRN staff and almost no comments from R&D staff.

Table 56: top 3 alternatives to research appointments (CRN)

CRN staff
1. Piggy backed to clinical care
2. Home visit
3. Overnight stay

1. 'Piggy-backed' to clinical care

Nine CRN staff made reference to research appointments being added onto routine appointments or clinical reviews being added to research appointments to reduce the requirement for 'extra' hospital attendance:

> *".. with a lot of my studies now, I've had a lot of people say to me, 'We will do the research, but can you try and fit it on a day we're already here?' (CRN-48)*

CRN staff also referred to 'piggy backing' of research samples, so samples were only taken at the same time as routine clinical bloods. This method of opportunistic sampling minimised infection risks and there was no additional pain or discomfort for participants:

> *"And we did get parents that would refuse you know, unless they were done at the same time as other bloods. So, it was a big thing that they **had** to be done when the bloods were done." (CRN-79B)*

All the comments related to this method of combining research and clinical care were positive and this definitely seemed to be viewed as a way of reducing recruitment difficulties:

> *"Yeah, in every sense... I would say, if you can piggy back research to their clinical care as much as possible, it's better all round." (CRN-88B)*

2. Home visits

Home visits were spoken about positively by 4 CRN staff to aid patient recruitment and retention to studies. Staff commented that avoiding hospital attendance was an incentive to some families. However, very few staff had direct experience of this and questions were raised about how that would work for higher risk trials.

3. Overnight stay

A study which required CYP to stay overnight as an inpatient was identified as extremely challenging, with one site identifying this as impossible:

> *"there was a cardiology study that we had to close before we even opened to recruitment. And one of the major factors was they needed a bed for PK overnight. And, the way the hospital is, and currently continues to be, you know the PI had to make decisions that this is never going to happen. We'll never have that bed to do it." (CRN-88H)*

There were however comments about strategies that had been developed to overcome these issues such as the use of local hotels for overnight stays. However, this was only feasible where the study was funded through industry.

8.3.4.4.7 Consider different approaches to traditional PK approaches

In order to overcome issues and concerns associated with the sampling requirements of a traditional PK study alternative approaches were discussed. *Figure 54* below summarises CRN staff attitudes towards a number of alternative PK methods. *Table 57* then summarises the top four approaches.

Figure 54: alternative approaches to PK study conduct (CRN staff)

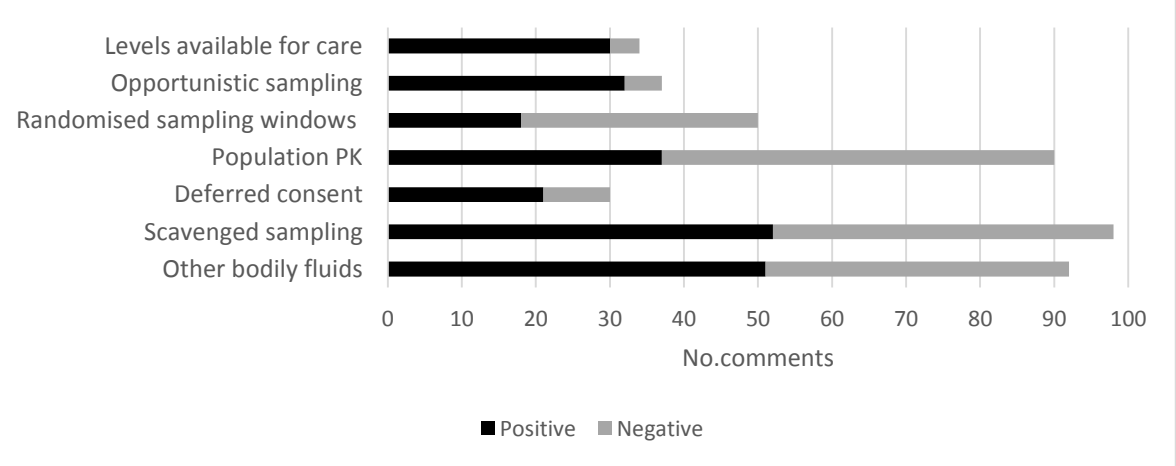


Table 57: top 4 preferences for alternative approaches to PK study conduct (CRN staff)

CRN staff preferences
1. Levels available for routine care
2. Opportunistic sampling
3. Deferred consent
4. Other bodily fluids

1. Make 'research' levels available for clinical care

Similar to CYP and parents, CRN staff felt very positive about the concept of making levels obtained within a study available for clinicians to potentially optimise patient care:

> *"I think it is a level of reassurance from both the clinical and the parental perspective because... you are taking this blood but you are getting the result and then you are acting on that, so I think that is reassuring for them" (CRN-45D)*

However, similar to nursing staff they were concerned if the results would not alter care delivery then clinical staff would not engage with the idea:

> *"If the doctors or whoever is looking after them believe that it is a key factor in their care and actually having those levels could help them and alter their care, maybe change it, definitely. But if it was seen as a bit wishy-washy… then it might not affect it" (CRN-78)*

2. Opportunistic sampling

Opportunistic sampling reflected samples taken alongside routine or clinically indicated samples. Overall this was a popular approach amongst research staff, with comments reflecting a belief that this reduced unnecessary sampling and therefore reduced infection risks. There was also a perception that parents would like this approach. However, staff concerns reflected that there would need to be monitoring on the overall number of samples taken i.e. the maximum number of samples /volume to be taken:

> *"I guess opportunistic sampling still has a number in terms of what we're looking for, four samples or six samples. So, it's just managing that alongside all the other bloods that they might have taken" (CRN-77)*

3. Deferred consent

Amongst the 24 participants where deferred consent was discussed, staff mostly favoured it as a positive contribution to PK research, particularly in emergency and critical care settings. Negative comments reflected anxieties about parents' reactions related to consent:

> *"I think it is so drilled into us that we don't do anything until we have got consent in research… I don't know why but it does not sit comfortably with me to do that" (CRN-95A)*

4. Other bodily fluids

There were a large number of comments about the use of other bodily fluids for measuring PK levels, either in a study comparing results to blood or as an alternative to blood. Overall staff were positive towards this method, with comments reflecting that CYP and parents would prefer non-blood sampling as it was less invasive and there was no pain associated:

> *<parents> "They're much happier if you put a pad in the nappy. Or they're happy for you to just collect from a catheter bag. They don't seem to be watching you as much as when you were taking a blood sample" (CRN-94)*

Where this was felt to be difficult was with an adolescent population, if specimen collection needed to be at specific times (particularly if not catheterised) or if large volumes were required, particularly in a neonatal population. Overall staff implied that this was not necessarily an easy option and there were concerns that it might actually be more time consuming for staff:

> *"I'm just thinking about blood versus urine, it's probably as time consuming as each other really, infection control procedures and such-like" (CRN-88H)*

Overall CRN staff valued approaches which could contribute to a population PK approach- such as scavenged samples, use of alternatives to blood and using research care to improve clinical management. R&D staff made very few references to alternative methods, focusing more on the challenges of protocol design.

8.3.4.4.8 Funding, capacity and target setting

R&D staff were concerned about the capacity of departments to deliver research to time and target. Adequate funding was therefore the crucial facilitator for approval, however there was also a recognition of utilising appropriate resources to support activity as well as ensuring that realistic targets were set at the beginning so a study could be seen to succeed:

"I think we've learned a lot from these types of studies and so whereas before in terms of targets setting, before we'd be you might have 10 patients within the department that would be eligible, we could get five of them. We're a lot smarter now, we would now probably say we can get one..." (RD-119B)

8.3.4.4.9 Patient and Public Involvement (PPI)

PPI was identified as a facilitator for PK research by R&D staff because it ensured that the study was both important and acceptable to CYP and parents:

"I think that's why consumer involvement is really important... because it's about seeing actually what parents and what children want to see done" (R&D-118)

This could also serve to address concerns associated with all stages of a research study.

8.3.4.4.10 CRN protocol review

In addition to involvement of PPI participants to review the acceptability of a study, there was also a recognition of the value of locally based CRN review. CRN staff described a vital role in reviewing a protocol to determine feasibility and acceptability in the local context:

".. sometimes you find yourself in these meetings going, "Your protocol is great. We can see what you're trying to do but actually in reality this is not going to work" …. The two don't always marry up very well; the nursing side of things and how we think and how somebody who writes the protocol might think." (CRN-77)

One of the main stumbling blocks was whether a study would clash with hospital policy or accepted local practice and there were several accounts from CRN staff of having to challenge the study sponsors over the study protocol:

"You do have to fit around your hospital policy. Because if anything went wrong, the first thing you do when you analyse an incident is, well were you doing something according to how we want it done at the hospital? And if you blatantly haven't, then you are on a sticky wicket" (CRN-88G)

Local CRN staff therefore played a vital role in determining the fit between a study protocol and local practices. Once a study was established as acceptable then planning and organising the study to ensure it ran smoothly became a priority.

8.3.4.4.11 Summary of facilitators

Many facilitators identified by CRN were similar to those identified by CYP and parents. Appropriate communication, consideration of 'the approach' and engagement with clinical staff professionals were all identified as positively enhancing the recruitment process. CRN staff also felt the optimum study design should offer some form of personal benefit and / or benefit to future CYP, samples would ideally be taken alongside clinically indicated samples or research samples would be used to inform clinical care and additional hospital appointments would be 'piggy-backed' to clinically indicated appointments. Consideration of analgesia and the promotion of safety were important facilitators. R&D staff focused on the adequacy of funding for research, careful assessment of capacity and the setting of realistic targets. CRN staff were recognised as being a valuable resource to assess the feasibility of research at the local level.

8.3.5 Medication

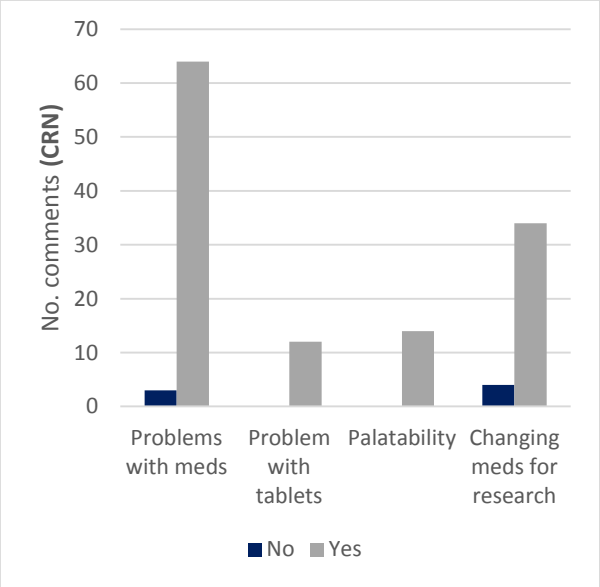
8.3.5.1 Barriers/ challenges with medicines

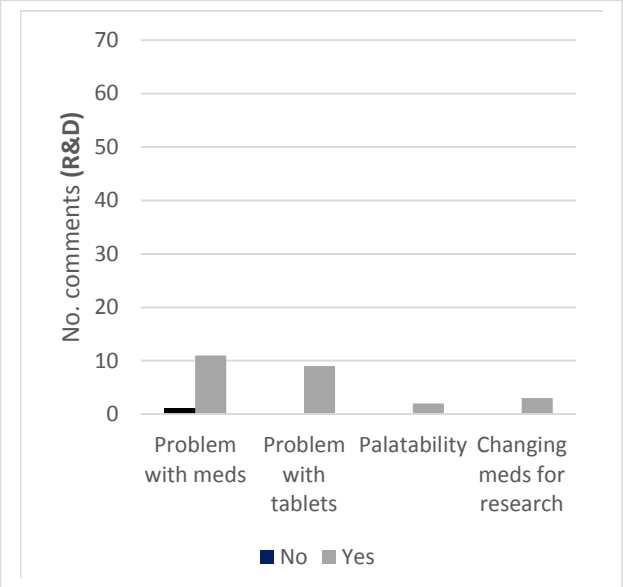
Research personnel were asked about their experiences surrounding the administration of medications to CYP. Barriers and facilitators are summarised in *Table 58.* Overall most of their observations were negative, predominantly reflecting problems encountered in drug administration (see *Figure 55).*

Table 58: summary of barriers and facilitators to administration of medications (CRN & R&D staff)

	Barriers	Facilitators
Medications	Accuracy with administration	
	Tablets/ palatability / changing for research	Pharmacy review

Figure 55: experiences and attitudes towards medications (CRN & R&D staff)





CRN staff recognised that taking medications was a significant problem generally and was a significant consideration in the conduct of PK studies:

> *"they fell at the first hurdle. If you can't get the drug in, you can't really go into a PK study for it." (CRN-72C)*

Staff commented on the level of planning that went into a study and the complications created when there was an issue with the medication itself or issues with fitting the medication into existing regimes:

> *"It's so much out of your control. You think you've covered it all and you're like, "Yes, I've got folders full of instructions on how to do this... and damn! The child won't take the drug, I didn't think about that!" (CRN-77)*

The issue of tablets was specifically referred to by 11 CRN staff and 4 R&D staff, with comments focusing on the size of tablets and children's ability to swallow them:

> *"Children don't suddenly become able to take or want to take tablets at once, like when they hit eight or something, you know" (CRN-88F)*

Palatability was similarly raised as a problem, with comments about the taste and smell of medications inducing nausea and vomiting and an aversion to oral medications:

> *"I've known of a study, I haven't worked on it. But there was a study where the medicine was so **awful** to taste they literally couldn't take it." (CRN-78)*

R&D staff commented that consideration of an appropriate formulation was an aspect that was often neglected in trial development. These studies then experienced recruitment or retention issues which could have been avoided if earlier consultation with a paediatric pharmacist had occurred. However, in spite of this there were reflections on the difficulties of changing a medication for the purposes of a research study if the current medication was seen as 'working' and the child was accustomed to taking it:

> *"...It is a tablet, whereas these families are used to these dissolvable tablets, it's a classic example, they're struggling to get parents to change that, even something as small as that. And they're really unwilling, families are thinking, 'No, I don't want to have to do that'..." (CRN-48)*

8.3.5.2 Facilitators with medications

The main facilitator identified from research personnel responses was for early pharmacist input to review formulation, administration and proposed regime.

8.3.6 Sampling

As with CYP, parents and nurses, research personnel made many comments about issues surrounding sampling for PK studies. Barriers and facilitators are summarised in *Table 59* below.

Table 59: summary of barriers and facilitators related to sampling (CRN & R&D staff)

	Barriers	Facilitators
Sampling	Capillary Cannulas	• Use of indwelling lines • Conduct on PIC
	Blood volumes & frequency	• Guidelines • Engagement with clinical teams • Consider alternative methods to reduce sample volume and number[1] ○ opportunistic sampling ○ other bodily fluids
	Sampling regime	• Training • Support from research teams

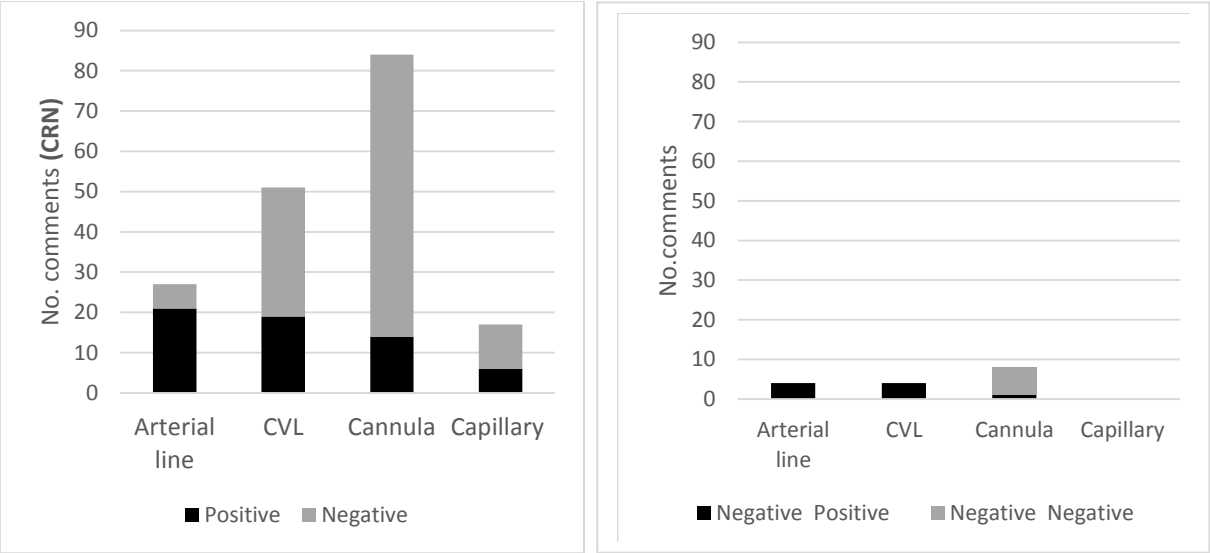
[1]See also section *8.3.4.4.7*

8.3.6.1 Barriers to sampling

8.3.6.1.1 Vascular access

The type of vascular access was frequently discussed by CRN staff but not by R&D staff. (See *Figure 56* below).

Figure 56: opinions on vascular access (CRN & R&D staff)



Capillary sampling was not widely discussed but negative comments reflected the pain and distress associated with both methods and issues about the reliability of samples obtained in this manner. Cannulas were widely discussed and although some staff discussed positive

experiences of obtaining samples from them, there were large numbers of negative comments (70 negative comments) reflecting that they did not bleed back well or for very long, siting them and manipulating them was traumatic, it was challenging to get the required volumes of blood required, siting two cannulas as specified in protocols was incapacitating, CYP often had 'poor veins'; with restrictions in where vascular access can be sited or because they were acutely unwell, siting them and manipulating them required skilled personnel and there was often no clear guidance for the care and maintenance of cannulas in protocols:

> *"...people I think have been misled by this simplification where they say, "Oh, it's only a teaspoonful of blood." But actually, from a small vein in a young child's arm, getting 5mls, a teaspoonful, is not as easy as it sounds. It's not until they try it that they appreciate how difficult it can be." (RD-119A)*
>
> *"Talking about PK studies... by definition, that involves taking blood and the big question is who's going to take it and are they available? Surprisingly few nurses are trained in venepuncture... Doctors are never available when you need them. And the phlebotomists, they're always complaining that they are overloaded". (CRN-77)*

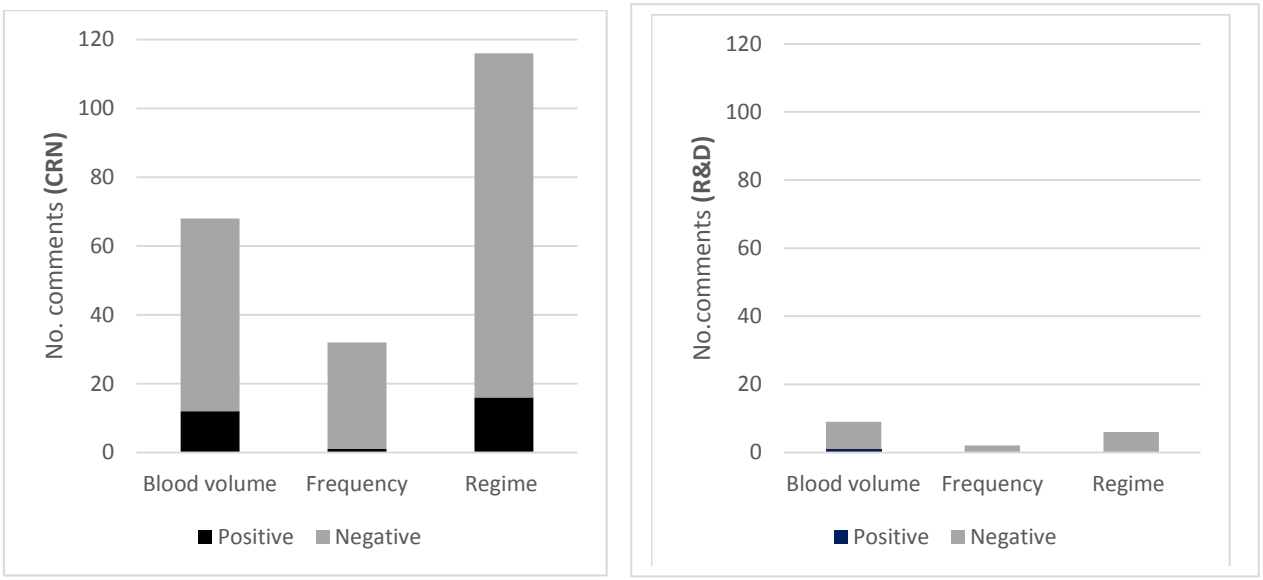
There were therefore a large number of barriers associated with the use of cannulas.

8.3.6.1.2 Obtaining samples

Similar to nurses, CYP and parents, CRN staff commented on blood volume, the number of samples and the required regime or sampling protocol (see *Figure 57* below). There were low volumes of comments by R&D staff. Similar to CYP, parents and nurses, research personnel commented more about the volume of blood being sampled, than the number of samples. Negative comments reflected perceived parental and staff anxiety about the volumes being sampled and a concern that these samples were in addition to clinically indicated samples:

"...you know, you're taking 20ml and you don't realise that the phlebotomist has got a form for another ten, so it's just on each patient, really weighing up how large they are, what problems they've got, is it safe to do so." (CRN-68A)

Figure 57: attitudes to study sampling requirements (CRN & R&D staff)



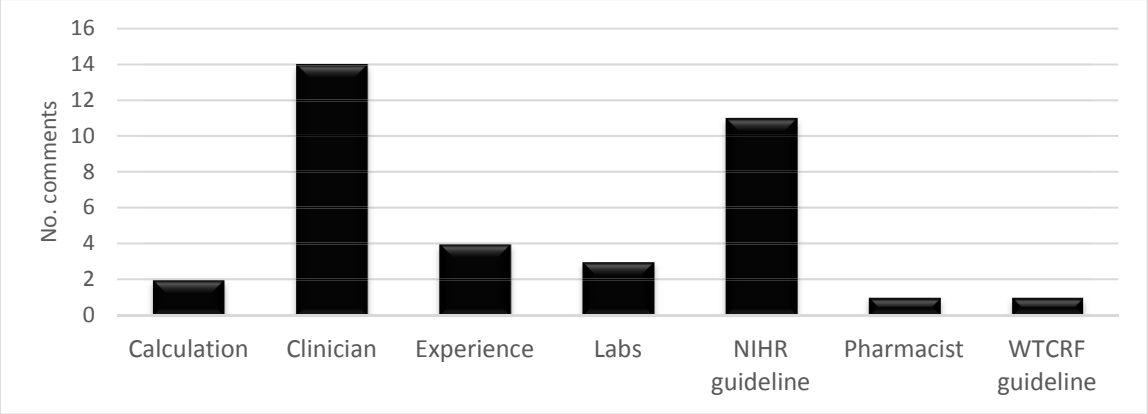
There was also uncertainty amongst research staff about acceptable sampling volumes, particularly studies which did not differentiate between participants based on age or weight. 19 /30 participants (64%) asked did not know of a protocol/ guideline to refer to:

"Do you know what, I don't, I just refer to the protocol and I hope … I suppose I have always presumed the protocol is right, that it has been through ethics and if they've approved the volume of blood then I go on that" (CRN-95B)

Where sources of knowledge were referred to (n=36) NIHR guidelines were the most reported guideline (n=11, 31%). However, reliance on clinicians (n=14, 39%) and personal experience was evident (n=4, 11%) (see *Figure 58* below).

"I also go on a bit of judgement as well, if you are looking at something and you know, thinking oh well that's actually quite a lot of blood… So, I think some of it has got to go with your clinical judgement as well." (CRN-95C)

Figure 58: sources utilised to determine acceptability of sampling (CRN staff)



Although there were fewer comments overall about the number of samples, all 31 comments on the topic were negative. Many of the comments reflected concerns that frequent samples exposed CYP to more pain and distress. A trial sampling regime was one of the most discussed aspects by CRN staff, with 41 / 43 participants commenting negatively about protocol regimes (100 negative comments). These reflected the specificity and inflexibility of many trial protocols:

> *"it's just all those unforeseen things, isn't it? It's the child that won't take the drug, it's the cannula that won't go in, it's the cannula that won't bleed back, it's the sample that you can only get half of what we need, it's the one that goes out of the window. It's the problem that crops up in labs when you forget to put the little sticker on that goes off to the companies…" (CRN-77)*

There were also numerous references to the challenge of matching staffing to the requirements of the protocol, particularly through the evening and overnight periods:

> *"And the timings of the sampling – the four hours, eight hours, 12 hours, 16, 24 – absolutely, I mean we don't … We haven't got the provision to do the night time samples". (CRN-95A)*

R&D staff were in agreement, highlighting the impact of the regime not only for CRN staffing, but also for the laboratories staff processing and storing samples. Overall both sets of participants were concerned about the impact of blood sampling on patients, particularly the total volume of blood required and the required sampling regime.

8.3.6.2 Facilitators to sampling

8.3.6.2.1 Use of indwelling, clinically indicated vascular access

Similar to both service users and nurses, CRN staff also spoke positively about the concept of sampling from arterial and CVLs; referring to their ease of use and lack of pain or inconvenience to the patient:

> *"It's easier if they've got central lines then you know that you're almost guaranteed to get your samples" (CRN-72D)*

However, with very few of the interviewed CRN staff assessed as competent to access arterial lines this was identified as a facilitator only in areas such as PIC or theatres. Similarly, staff were not necessarily competent to access all forms of CVL, for example vascuports or port-a-caths. There were also concerns that accessing CVLs for research purposes placed the patient at increased risk of infection:

> *"I think some parents are really funny about how many times the line's accessed" (CRN-88D)*

Utilising indwelling, clinically indicated vascular access devices were therefore identified as a facilitator, however CRN staff cautioned that this was subject to staff having the right training and competence to be able to utilise the lines.

8.3.6.2.2 Reference to guidelines

As outlined in section *8.3.4.4.7,* alternative approaches which reduced the requirement for samples or considered the use of non-blood sampling were viewed as potentially facilitative. Despite concerns about the total sampling volumes required few participants utilised or were aware of guidelines to assess acceptability. Protocols which reference guidance on acceptable volumes are welcomed by many participants (28/ 30) (93%):

"We couldn't get an answer... it was all over the place, and everyone was saying different things, it would be nice, yes, definitely, to have something to think, 'Yes.' You feel confident when you've got guidance and you've got boundaries" (CRN-48)

Reference to guidelines therefore appeared to be a strategy valued by both parents and research personnel.

8.3.7 Processing

Similar to all the participant groups, CRN and R&D staff did not highlight large numbers of barriers with the processing of PK samples. Barriers and facilitators are summarised in *Table 60* below.

Table 60: summary of barriers and facilitators in relation to processing (CRN & R&D staff)

	Barriers	Facilitators
Processing	Documentation accuracy	• Training • Trial related paperwork / documentation • Laboratory staff involvement

Negative comments reflected similar issues to nursing staff related to problems with the opening times of laboratories or issues with the timeliness of feedback on levels:

"Also, vancomycin being given and… when the level finally comes back it was high but because it didn't come back in time they had already had another dose on top of that." (CRN-45B)

CRN staff also raised concerns that current documentation of sampling would be insufficient for studies utilising scavenged samples or opportunistic sampling:

"Yes, you also then run the risk of them writing either the wrong time just to please you or not giving a time at all which we have found previously with samples. There has been no time or date recorded" (CRN-45C)

R&D staff also commented that funding cuts had severely affected laboratory resources which could impact on successful study conduct.

Key facilitators were therefore the training of clinical staff to ensure accuracy of documentation, the development of trial paperwork to aid documentation and the involvement and support of lab staff:

> *"We're always very well prepared with the labs…* [from labs] does some amazing labels for us as well that clearly show his staff, and us, what to do and that's a massive help" (CRN-48)*

8.3.8 Outcomes

8.3.8.1 Barriers to successful retention and completion of a trial

Key barriers and facilitators are outlined below in *Table 61.*

Table 61: summary of barriers and facilitators related to study outcomes (CRN & R&D staff)

	Barriers	Facilitators

Outcomes	Clinical nurse prioritisation and responsibility	• Engagement with clinical teams
		• Research culture
		• Support:
		  ○ Outreach support
		  ○ Dept. specific team

	Research staffing levels	
	Attitude to research	Research culture

8.3.8.1.1 Clinical nurse prioritisation and responsibility

Throughout the interviews and focus groups there were numerous references from research personnel about the existing workload of clinical staff and their ability to carry out 'research care':

> *"We can't get away from the fact that the nurses are **over-stretched.** The clinicians are completely **over-stretched** and I think to take on any more, there's quite a lot, it's a big ask, a **huge ask** in this climate. And actually, even if you just get us, get a designated research personnel doing those things, there's a huge sense, you get more support" (CRN-88B)*

CRN staff appreciated that clinical staff prioritised clinical care requirements and as a result research care was a lower priority:

> *"I remember a clinical study that was going on and there was you know, there was breaches in protocol and stuff but I didn't see that as the bedside nurse's fault*

because her priority was, and quite rightly should have been, looking after the patient and not trying to reiterate protocol." (CRN-88C)

The frustration for research staff was trying to ensure that all the patients' needs were met, particularly when time and energy had been invested in setting up and planning a study. If research tasks were delegated to clinical nurses who were juggling multiple commitments there were concerns these would get missed or completed incorrectly:

"I think ideally if it could all be done by the research team that would be great because you'd have a fairly accurately followed protocol. I think as you dilute it down and delegate roles, then you don't get the protocol followed as much..." (CRN-45B)

CRN staff wanted to be able to support staff by conducting the research components of the job, leaving clinical staff to provide 'clinical' care and there were examples of staff working long hours to try and cover all research activities. The challenge was that this was not sustainable and many teams could not provide this level of support.

8.3.8.1.2 Research staffing levels

Research staffing requirements were one of the most discussed topics by both participant groups, with 73 comments from CRN staff and 23 comments from R&D staff. Not surprisingly given their concern about clinical staff ability to undertake research activity as well as clinical care, the biggest concern was the provision of cover for PK studies outside of office hours- 'out of hours cover'. Even within designated facilities such as WTCRF, staff felt it was a challenge to facilitate PK research on an ad-hoc basis:

*"We do offer a 24/7 service **as** and **when** we need to. But, if you said the patient is coming in tomorrow to start that drug and have PK sampling, the repercussions of that are quite big really… you potentially have maybe up to six staff to move around." (CRN-77) (senior member of staff within WTCRF)*

Flexible cover was an issue, even for a team which provided seven days-a-week cover such as the PIC Research team. At the present time no team felt they would be able to provide the flexible 24/ 7 cover a PK study would require on their current staffing:

> *"I think at the moment there's not enough of us at the moment to cover a 24-hour service. I heard it mentioned and I thought, 'There's only seven of us, so to cover-,' (laughter) I don't quite know how you'd work that one out..." (CRN-48)*

There were also safety considerations with the administration of potentially novel medications as part of PK studies. Staff cited the importance of ensuring trial activity was planned as much as possible for office hours in the event of an emergency:

> *"we don't like to really be administering a drug in the middle of the night and that sort of thing. Particularly if it's a drug that a child has never taken. So, you want that kind of infrastructure around you and being able to yell on down the corridor 'just give me a hand with this'… so we always want our high-risk stuff to be in those daytime hours" (CRN-77).*

8.3.8.1.3 Attitude to research

A number of CRN staff reflected on challenges they had encountered with obstruction and negativity from clinical colleagues:

> *"It is a teaching hospital however, the archetypal nurse who's been qualified for 40 years doesn't want a bead of it... honestly. They don't want to touch it with a barge pole because it's more work on top of their normal workload. "(CRN-88C)*

Research staff felt that the work they were doing was important but felt there were significant organisational barriers from small numbers of negative clinical staff.

8.3.8.2 Facilitators for outcomes

8.3.8.2.1 CRN role

As described in section *8.3.4.4.10,* a key facilitator was the early involvement of a CRN to review a study protocol and determine local acceptability. This pivotal role extended beyond helping with recruitment. 25 CRN staff and 3 R&D staff made reference to successful study outcomes- medications given on time, samples taken, participants completed the

study- dependent on effective planning and organisation by CRN staff. Anticipation of potential problems was felt to be a key responsibility, with consideration made to anything that could influence the study conduct, including conflicting medications, the timing of procedures, physical space as well staffing requirements:

> *"Everything has to be planned, because obviously, it's all different times... Planning is absolutely **crucial."** (CRN-78)*

Precision was also a key factor for a successful PK study outcome, in particular the accuracy of medication administration, sampling and the accompanying documentation:

> *"A lot of it is down to the second... we are looking to the clocks to the second... We do our very best to do it at the right time… I think on here, you just are aware of how important it is to be so precise" (CRN 72D)*

Staff felt huge pressure to avoid inaccuracies or missing data and there were accounts of staff working long hours on overtime to ensure a protocol was followed:

> *"those weeks when I have had patients in outreach, I've been known to do 50 and 60 hours... it's my job. I've got to make sure it's okay, because ultimately if the sample is missed... ultimately we're the ones that have to explain it and fill in those gaps" (CRN-77)*

These facilitating behaviours or roles CRN staff played in the set up and conduct of PK research were therefore felt to have a crucial impact on the outcome of a study. These roles were not specific to PK studies, but staff identified that PK studies were dependent on a number of these factors. These aspects are summarised in *Figure 59*.

Figure 59: pivotal roles of CRN staff in the set up and conduct of PK research

8.3.8.2.2 Clinical engagement

There were 83 comments from 24 CRN staff about the importance of engagement with clinical staff and the development of good working relationships. When research staff were visible and interacted with clinical teams, this not only helped to promote safety but also promoted support for a study, mediated against 'gatekeeping' and helped with the portrayal of research to CYP and their families:

> *"...If you have a clinical team that's signed up to something because they appreciate..., for evidence based care, you can't just carry on giving X drug willy nilly without knowing how it's working. If that is part of the discussion with the family and the child, they see much clearer why there is a need for these type of PK studies" (CRN-88F)*

This was important at all stages of research conduct.

8.3.8.2.3 Research culture

Not surprisingly for people employed to work in research, most of the research staff felt conducting research was important. Comments reflected the value in developing treatment options, that research led to improvements in patient care and that it generated income:

> *"Any research means that you're wanting to improve a certain service or certain area. So, I think it's worthwhile. If it brings in the big bucks then obviously, it's even higher on the agenda." (RD-118)*

However, the crucial facilitating factor was that this positivity was part of a strong research culture, where staff valued the place of research alongside, or even as part of, everyday work:

> *"It should be part of normal care. Research should be just something that everyone does. I think in practice it's a lot of work to make that happen." (CRN-94A).*

CRN staff viewed themselves as having an important role to play in contributing to this culture:

> *"We go on about being a teaching hospital, as research nurses our responsibility is to **teach** research. To **promote** research to all. To help them, to enable them, to take it on in their very, very busy work schedules." (CRN-88B)*

8.3.8.2.4 Feedback from research

As part of a strong research culture there was a recognition of the importance of providing feedback from research findings to not only study participants, but also to clinical staff:

> *"They should be informed, because they're contributing because they want to help other people and they want to know that it's going to make improvements in the future so I think they need to be involved a bit more and not just left after we've got what we wanted." (CRN-48)*

Feedback ensured that the contribution of everyone concerned with the conduct of a study was recognised and valued.

8.3.8.2.5 Support

The biggest facilitating factor for the conduct of a PK study from both CRN and R&D perspectives, was designated research staff support. When this support was provided on an external outreach basis, CRN staff identified different strategies to help synergistic working.

One strategy was to 'join in' with the clinical team to help them with routine care in between research jobs:

> *"I used to end up making beds and checking drugs and doing everything with them, just so they could see I wasn't going to just sit and point the finger." (CRN-88C)*

Alternatively, staff took on roles which were clinically indicated (but had research relevance), to reduce staff workload. Adopting these strategies and becoming 'accepted' was an important step, not just for the individual research nurse, but for research activity:

> *"It does feel like you've 'broken in' doesn't it? When you've conquered an area and they accept you. You do feel quite triumphant that research is taking place" (CRN-88E)*

Similar to the nursing staff, CRN staff recognised that although clinical staff were grateful for any support, there were challenges to utilising a model of outreach research support. Some felt that clinical staff did not understand or respect their role and at times could experience being made to feel unwelcome and uncomfortable:

> *"How we all do when there's a foreigner on the ward! They end up following you around the ward like, "Who are you? What are you doing?" You feel uncomfortable" (CRN-78)*

Staff were also daunted by having to go into different environments, particularly highly technical environments such as PIC when they were not trained in the speciality:

> *"I think I'd have to have more specific training, I wouldn't want to go to and just access any random central line, and also **it's ITU!**" (CRN-67)*

There was widespread support for a department specific research team, not only from those who worked in such a team (5 from PIC, 3 from NIC and 1 from Burns team) but also from those working for 'generic' research teams (NIHR and WTCRF staff). Where this resource existed, it was felt to offer huge advantages to research delivery:

*"if you've got research coordinators and research nurses embedded in different departments and they're part of multi-disciplinary teams and they discuss the trials that are open and discuss responsibilities with people… if it was more like that, in **all** departments then you would have a better stream of communication and better delivered studies." (RD-119B)*

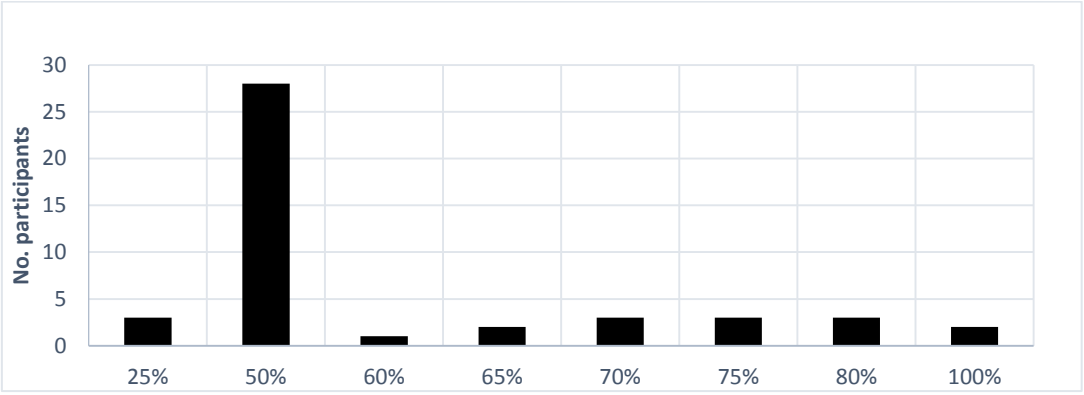
8.3.8.2.6 Model of support

There was widespread support from CRN staff for the conduct of PK research, with 41/43 CRN staff stating they would look after a patient in a PK study (1 did not answer; 1 had to leave the interview early) and 3/4 R&D Committee participants were similarly supportive. With reference to the PK study within the vignette (sampling over 24 hour period), two participants (CRN) felt research staff should provide 100% cover, reflecting concerns about missing data:

"because they don't see the data queries that come through, it doesn't impact them… they don't deal with the trials units… The importance of it is not always reinforced to them. You can say it is really important but they don't get the extra workload and they don't answer to them" (CRN-45B)

59% of staff (both CRN and R&D staff) felt support should be offered at a *minimum* of 50:50 shared responsibility between clinical and research staff, in order for the study to run successfully (see *Figure 60* below).

Figure 60: 'ideal' research: clinical staffing ratios for PK research (CRN & R&D participant responses combined)



8.3.8.2.7 Summary of facilitators for outcome

To facilitate the successful conduct and completion of a PK research study, key factors were the cultivation of a research culture, engagement with clinical staff and crucially research support. R&D staff emphasised the benefit of utilising WTCRF facilities or obtaining support from outreach services to facilitate research activity. However, CRN staff advocated wherever possible to utilise the support of an embedded research team.

8.3.9 Context

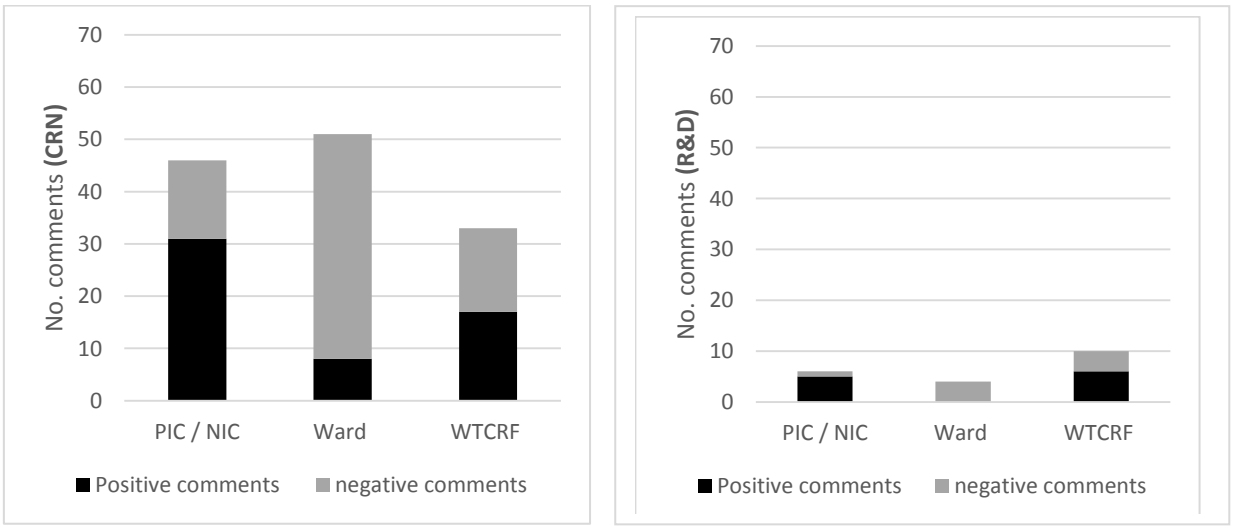
8.3.9.1 Barriers to context of research

Participants' comments on the conduct of PK studies reflected three main areas: inpatient wards, WTCRF and Paediatric or Neonatal Intensive care (see *Table 62* below for a summary of barriers and facilitators and *Figure 61* below for a summary of comments).

Table 62: summary of barriers and facilitators to the context of research (CRN & R&D staff)

	Barriers	Facilitators
Context	Wards	• WTCRF • PIC

Figure 61: attitudes towards the context of PK research (CRN& R&D staff)



Neither CRN or R&D staff had a favourable view of conducting PK research within inpatient ward areas. Concerns raised focused on a lack of space to conduct research, the noise and lack of privacy of ward areas and the challenge of complying with protocols within this environment:

> *"I bet there wasn't a single patient that all samples were taken correctly on the ward. Was there? Throughout the study" (CRN-45A)*
>
> *No, probably not" (CRN-45C) (Exchange between two PIC CRN staff).*

The use of designated research facilities was recognised as being a logical context for PK study conduct. However, research with hospital inpatients, studies which required sampling throughout the 24-hour period and studies which could not be advance planned were problematic.

8.3.9.2 Facilitators to context

CRN and R&D Participants overall were most positive about the idea of conducting PK studies in PIC or NIC environments. Positive comments reflected the fact participants had vascular access for sampling, staffing ratios were 1:1 and staff perceived there to be time to talk to families:

> *"When I first read it, it struck me … if they were in intensive care this would be much more acceptable and easier (sounds of agreement) because you have got the arterial line, you have got the nurse there, one to one. You know, they could just go through that on their shift and say they need these bloods then, then, then and then. To me, in my head, being an ex-PICU nurse, it is much easier and achievable than on a ward" (CRN-95A)*

Despite concerns about the vulnerability of families and the nature of research in the context of emergency situations, there was support overall for PK research within the PIC context. Conduct of PK studies within WTCRF was recommended for studies which could be conducted on an outpatient basis with advanced notice.

8.4 Mapping to I-PARIHS

The key aspects for the CRN and R&D participants were mapped to the Integrated PARIHS framework (Harvey and Kitson, 2016). See *Figure 62* and *Figure 63* below.

Figure 62: summary of CRN staff responses mapped to I-PARIHS

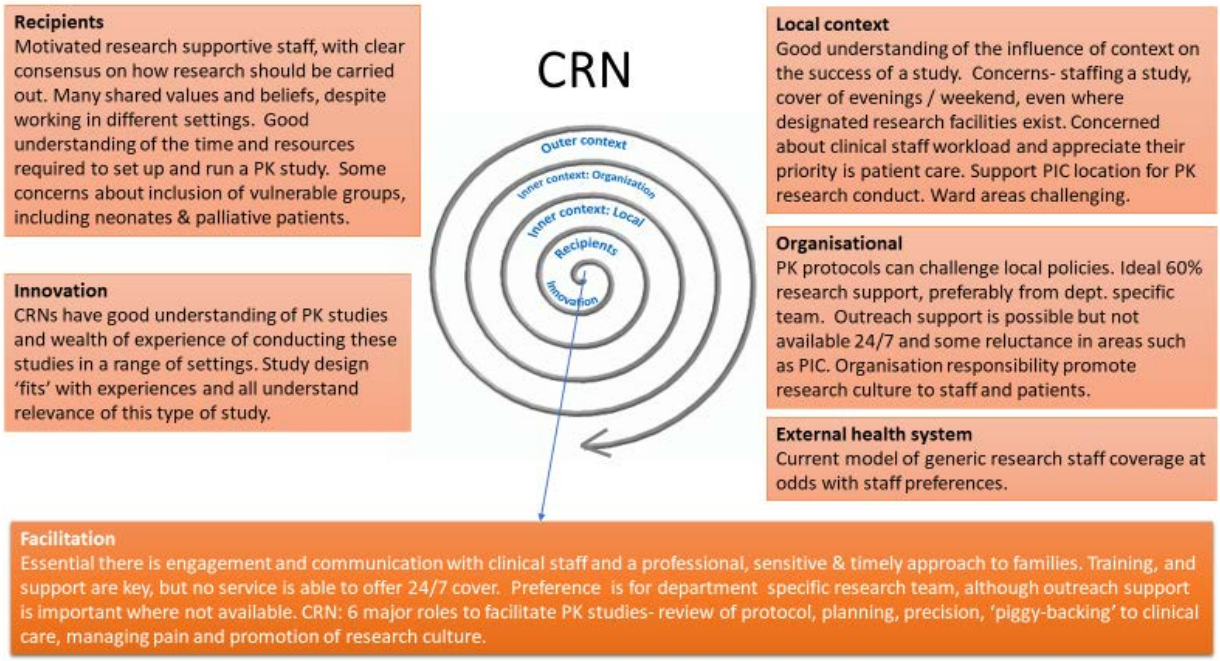
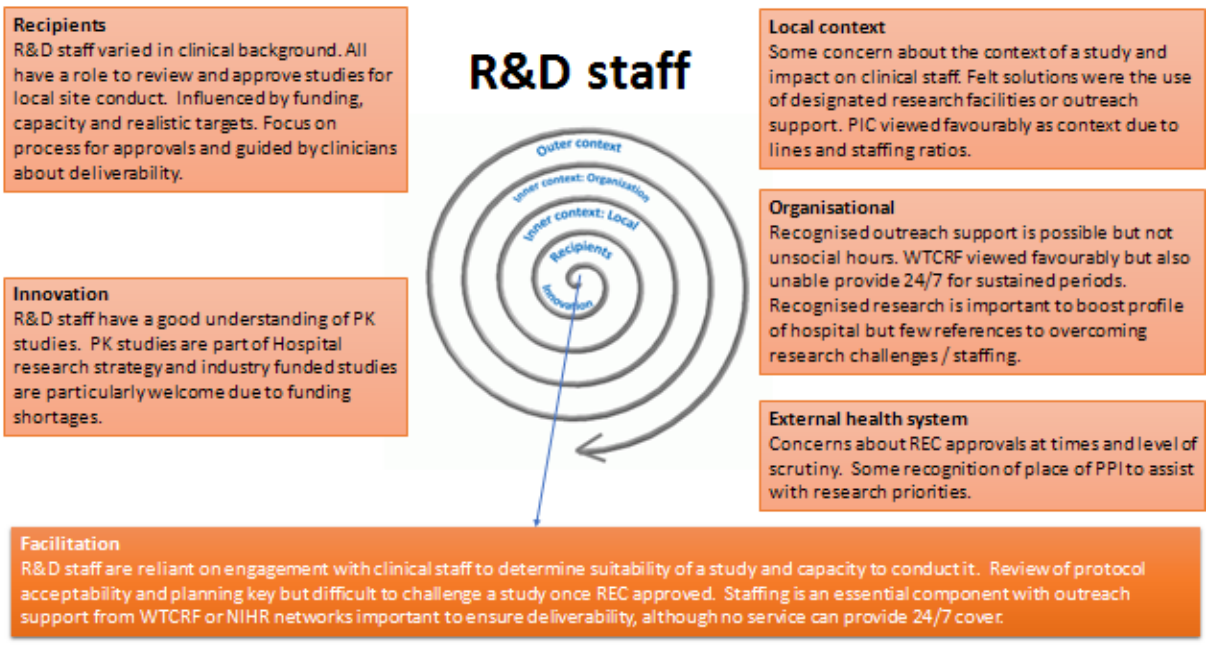


Figure 63: summary of R&D staff responses mapped to I-PARIHS



8.5 Discussion

8.5.1 Perception of families' decision-making

Staff from both participant groups felt parents' decision-making about participation was influenced by the type of study they were being recruited to, particularly if it offered a novel treatment option, and the concept of improving their own health. However, responses from CYP and parents, reported they were most motivated by the concept of helping others. This suggests that research personnel perceptions of patients' and families' motivations are not aligned. This could influence the way staff approach or discuss research with families, or even influence who they invite to participate, particularly if they are perceived as vulnerable (Kendall et al., 2007). Research nurses can experience significant discomfort and difficulty approaching patients to discuss recruitment, to the extent that eligible patients are not approached (Donovan et al., 2014). Research staff also influence recruitment 'cherry-picking' patients to increase the chances of good outcomes, and avoiding patients thought to be 'unreliable' (Lawton et al., 2012). These issues were raised by participants in PRESCRIBE, who expressed concerns about approaching vulnerable groups, families in challenging situations such as an emergency / life-threatening situation and avoiding families who failed to comply with treatments. These findings are of concern because they indicate that CRN staff could restrict who they approach to participate in future PK studies. This comes at a time when despite campaigns emphasising that the public can seek out research opportunities (National Institute for Health Research, 2013), less than 21% of the public report they would feel confident to do so (National Institute for Health Research, 2015b). Researcher-initiated approach to recruitment therefore still dominates and this could be compromised if researchers limit the inclusive approach. This approach is also not

welcomed by CYP and parents, who value the opportunity and choice to participate (as identified in chapter 6).

8.5.2 Research personnel priorities

When discussing perceptions of a PK study R&D participants were focused far more on aspects associated with finance, resources and targets. This is perhaps not surprising in a backdrop of declining clinical trials in the UK and blame being attributed to local NHS R&D approvals processes (House of Commons Science and Technology Committee, 2013). Research in this area has focused on identifying the impact of delays from the R&D approval process (Al-Shahi Salman et al., 2007, Hackshaw et al., 2008, Mallick and O'Callagan, 2009, Snooks et al., 2012), rather than *why* there are delays within this process. Despite the significance of the approval role R&D has, R&D participants within PRESCRIBE reported feeling relatively powerless. They reported feeling dependent on clinicians to highlight the feasibility and capacity of the organisation to conduct a study, but felt the pressure fell on them when a study failed to deliver recruitment to time and target. Recommendations from R&D staff reflected getting the right people or facilities on board and making sure that appropriate targets had been set so the study could 'succeed'. Little research has been conducted with those in a regulatory role at a local NHS Trust level so there is little with which to compare these responses. The findings from PRESCRIBE indicate there are multiple competing demands for those in regulatory roles in R&D and further work to explore decision-making would be of benefit.

8.5.3 Role of the CRN

As with the other PRESCRIBE participants, key facilitators of effective communication and engagement with families and research staff, reduction in additional burden for families and

training and support for clinical staff were identified. What was different was that research personnel encapsulated these aspects into the roles and responsibilities of the research nurse. The CRN role was therefore highlighted as the pivotal facilitator for PK studies. Within the published literature there is a growing recognition of the role of the CRN in research delivery (Mori et al., 2007, Gibbs and Lowton, 2012). Whilst some authors have emphasised the role of the CRN in writing protocols (Pick et al., 2011), there is a suggestion that their local expertise and knowledge is well-placed to review the enactment of a study protocol within the local organisational context. Organisational features such as referrals, clinic sizes, previous experiences, as well as resources, staff time and institutional identity can significantly impact on local conduct (Krein et al., 2010, Lawton et al., 2012). By reviewing protocols for acceptability, determining feasibility at the local site and identifying factors both congruent and incongruent to the organisation, difficulties associated with patient accrual could be overcome (Grunfeld et al., 2002, Kasenda et al., 2014, Pica and Bourgeois, 2016). The potential for CRN staff to contribute actively to discussions about the feasibility and acceptability of research is therefore apparent. CRN's have been identified as integral to the success of NHS research (UKCRC Subcommittee for Nurses in Clinical Research Workforce, 2007) and findings from PRESCRIBE support this.

8.5.4 Role conflict

As recruitment to clinical trials is increasingly placed in the hands of research nurses (Pick et al., 2011, National Institute for Health Research, 2016d) understanding their perspective becomes increasingly important (Grunfeld et al., 2002). Participants within PRESCRIBE had all worked as nurses first before joining research teams and many identified themselves as paediatric nurses first; research nurses second. Many research nurses, regardless of their

employment basis, saw research roles of lower status and asserted the primacy of their clinical or caring role (Donovan et al., 2014, Tinkler et al., 2018). This could be challenging for those with split roles who continue to work as a member of the clinical workforce and as a CRN or for staff who work with populations with greater mortality/ morbidity. Staff can feel conflicted about the impact of strict protocolised RCT requirements and the inconvenience trial participation brings for patients and jeopardise the integrity of the recruitment process (Lawton et al., 2012, Lawton et al., 2015). It therefore follows that a strategy of CRN staff operating on an outreach basis could potentially reduce role conflict. However, PRESCRIBE participants were far more supportive of a department-specific CRN team. Even staff who worked for the NIHR networks appreciated the value of staff embedded within a department with enhanced knowledge of the clinical speciality. In light of the findings from PRESCRIBE further work to compare and contrast models of working and the impact of these on clinical and research staff satisfaction is warranted.

8.5.5 Engagement with clinical teams

With no research service able to offer 100% cover, research personnel identified that engagement with clinical teams was vital for recruitment, patient safety and successful study outcome. This is supported by a recent meta-analysis, which identified that successful clinical research was dependent on the engagement of researchers, clinicians and patients (Newington and Metcalfe, 2014). Good working relationships between research and clinical teams and minimising the burden on local collaborators leads to good working relationships (Campbell et al., 2007, French and Stavropoulou, 2016). These findings are evidenced in behaviours described by CRN staff in PRESCRIBE, who reported helping with clinical care, taking routine samples alongside research bloods and developing tools to assist clinical staff,

in order to create good working relationships. However, there were reports of feeling like an inconvenience and having to work hard to gain support from clinical colleagues and these challenges are also recognised within the published literature (Tinkler et al., 2018). Relationships with clinical colleagues are fundamental for success in recruitment and successful study completion. Ultimately with clinical staff working close to maximum capacity there is a danger that clinical staff will feel pressurised by additional requests and research staff in PRESCRIBE recognised this. This must be reflected in future research resource planning and allocation.

8.5.6 Research services planning

The largest concern for CRN and R&D staff about staffing centred on the support of clinical colleagues and the provision of support outside of office hours. None of the interviewed teams were able to provide 24 hours a day research support, especially for a study design that did not permit advanced planning. This has serious implications for the conduct of all clinical research activity, not just PK studies. There are huge cost implications for low enrolling studies as well as the implication of no scientific benefit gained (Kitterman et al., 2011). A study examining the recruitment success of Medical Research Council (MRC) and Health Technology Assessment (HTA) funded trials found only 55% of studies recruited their target sample size and 45% needed an extension of time or funding (Sully et al., 2013). The discontinuation of trials raises ethical concerns and wastes scarce research resources (Kasenda et al., 2014). Despite this there is little examination of the staffing resources required to undertake clinical research activity and no published evidence for staffing ratios or models of working. Staff within PRESCRIBE recommended research cover for a PK study for an average of 57% of the time, including weekends. The evidence from participants in

PRESCRIBE from across the West Midlands and South West England is that this resource is not available. This has the potential to significantly impact on successful study delivery.

8.6 Limitations

8.6.1 Participants

The original plan to interview 7-8 CRN staff was rapidly revised, once the diversity of the CRN team was fully appreciated. The work then developed into a multi-site study to capture perspectives from teams working in emerging areas of interest, such as neonates and staff covering a wide geographical area. This was of enormous benefit to the perspectives captured, however it did add significantly to the time required for study conduct with application for amendments through IRAS and negotiating NHS R&D approvals. It also added significantly to the workload of transcription and analysis although this did mean that saturation was achieved.

It took some time to determine the best representatives for staff identified within the PPI work as 'Hospital Managers'. Once this was established as members of the R&D Facilitation Committee, negotiating access proved challenging. Despite several personal discussions and emails, the sessions took over one year to set up and was then rescheduled twice. Negotiating with gatekeepers was challenging and for the future, a variety of methods and utilising the support of senior staff should be considered.

Whilst some CRN staff (n=4) and R&D staff (n=1) did speak of their own experiences of being a parent of a CYP taking medications or experiencing invasive investigations, this information was not collected as part of the demographic data. As there were low numbers of comments reflecting personal challenges it was felt unlikely to have compromised interpretation of staff attitudes.

8.6.2 Subject matter

The interview schedule was tailored to each professional group and their roles, therefore there were some small differences in the questions posed to CRN and R&D participants, although the same vignette was utilised. In 2013/ 2014 when the interviews and focus groups were being conducted there were widespread criticisms of the research governance system (House of Commons Science and Technology Committee, 2013). Huge changes in the local R&D structure and staffing as well as in the Health Research Authority (HRA) funding and approvals process followed shortly after. The interviews therefore span a period of significant change nationally and locally which might limit the applicability of the research in 2017.

There were references from R&D participants' to the place of commercial PK studies, for commercial value and income generation. Some CRN staff also highlighted working on commercial studies, particularly the WTCRF. However as participants' did not differentiate between the design and conduct of commercial vs non-commercial studies this issue was not explored in detail.

8.7 How does this qualitative work with research personnel address the gap in knowledge surrounding pharmacokinetic research?

Chapter 8 set out to address gaps in knowledge associated with research personnel perspective, the influence of context and facilitation and has addressed all three aspects.

1. The existing literature suggests CRN staff could play a pivotal role in the conduct of PK research, particularly with recruitment and obtaining informed consent (Connolly et al., 2004, Nagel et al., 2010, Lawton et al., 2012). However, there is a paucity of research

surrounding the attitudes of paediatric research staff and none undertaken to review attitudes towards PK research conduct. PRESCRIBE therefore makes an important contribution to the current evidence base with 43 representatives from embedded research teams, research department specific staff and NIHR research network staff from two of the largest UK Children's Hospitals and a tertiary Neonatal Hospital. With enhanced understanding, measures to assist with research conduct can address both PK recruitment and study retention.

There has been very little work to explore the research approvals process at local NHS sites; known as R&D approval (National Institute for Health Research, 2016e), particularly surrounding decision making by R&D staff. PRESCRIBE is the first study the researcher is aware of to conduct interviews with representatives at local NHS level to explore their views on the approval and conduct of paediatric research. Although only four participants were interviewed this work makes an important step towards understanding more about the role of key personnel involved in the R&D approval process and factors influencing their decision making.

2. There are suggestions that local context has a large influence on the conduct of research (Krein et al., 2010) and participant reports within this study support this. However, little work has been undertaken to examine the impact of research configuration, staffing ratios and local context. PRESCRIBE provides important evidence that utilising designated research facilities is not a panacea for the challenges of conducting PK studies, although they are useful for the conduct of studies on an outpatient, Monday-Friday basis. The study has also

established there is support from research staff for the conduct of PK studies within the PIC and high dependency context which has not been reported before.

3. The third gap in the knowledge this work addresses is the identification of facilitators for future study design and conduct. Key facilitators are the development of good working relationships between clinical and research personnel, working together to ensure successful trial conduct. Research support is fundamental for success, ideally from a department specific research team with minimal additional samples and hospital attendances. Although these findings focus on PK studies, there are observations which appear to be relevant to all paediatric study designs which involve biological sampling, detailed protocolised care and timely interventions.

8.8 Conclusion

Research staff are a highly knowledgeable resource for the conduct of PK studies and have a multitude of experiences to draw upon. They are supportive of future PK research but this is highly dependent on the context and type of study. Studies in rare diseases which can be planned meticulously in advance can be accommodated within designated research facilities (where these exist). However, PK studies which have no personal benefit to participants are more problematic. Where PK studies are conducted in clinical areas there are likely to be significant issues in study conduct, particularly in the context of ward areas. Conducting research in PIC is a concern to many research staff, due to the acuity of the patient and concerns about parental anxiety (Siner et al., 2014). Despite this, there is support for PK research at this time due to the availability of sampling lines and because analgesia is usually optimised. A model of approximately 60% research staff cover is the preferred model for support, however there is a recognition that few research services are able to provide this.

In addition, there are concerns about the ability of outreach support in areas such as PIC to meet research requirements. The current model of generic research cover is therefore at odds with service user and staff preference for embedded research teams and this renders supporting these studies challenging. Given the huge problems that exist with studies discontinuing and failing to recruit (Kasenda et al., 2014, Pica and Bourgeois, 2016) a key requirement is to ensure studies are appropriately funded and resourced with appropriately trained research staff competent to practice within the study context.

Chapter 9: What is known about the attitudes towards and barriers and facilitators to pharmacokinetic research: discussion and conclusions

9.1 Introduction

The purpose of PRESCRIBE was to establish the perspectives of stakeholders and understand more about the barriers and facilitators to conducting PK research. The aim of chapter 9 is, using an implementation science model, to collate, compare and contrast the results from chapters 3-8 and summarise participants' attitudes towards PK research and the barriers and facilitators to conducting PK studies. From this, evidence-based guidelines for future researchers are developed (see Chapter 10).

9.2 Implementation science

Implementation science models are recognised as being useful to promote the systematic uptake of research findings and other evidence-based practices into routine practice (Eccles and Mittman, 2006). One of the key ways they are used is to identify key constructs that serve as barriers or facilitators (Nilsen, 2015, Birken et al., 2017) and PRESCRIBE has adopted the I-PARIHS approach (Harvey and Kitson, 2016) to frame an evaluation.

9.2.1 Evidence /Innovation

Innovation is evidence derived from research, clinical and patient experience (Harvey and Kitson, 2016). The higher the level of evidence across all three aspects, the stronger the evidence is regarded as being and the more likely the implementation will be to succeed (Kitson et al., 1998a). PRESCRIBE commenced with a scoping review of published PK literature with broad inclusion criteria to identify the existing knowledge base surrounding

PK research design. The evidence was found to be weak; with no systematic reviews of the topic, no identification of factors facilitating conduct and a lack of standardisation to PK reporting. The scoping review therefore makes a major contribution to the knowledge surrounding barriers to PK conduct through the categorisation of 5 major themes and a crude indicator of the scale and magnitude of each problem (Chapter 3). Following this a thorough exploration of who the stakeholders were, how to engage with them and the best methods to use was conducted (Chapter 4) before in-depth explorations of their perspectives (Chapters 5-8). The evidence has therefore been developed through a combination of explicit knowledge, tacit practice-based knowledge and patient experience.

9.2.2 Recipients

This construct considers the impact individuals can have in supporting or resisting an innovation though their views, beliefs and established ways of practice (Harvey and Kitson, 2016). In recognition of this, understanding the views of stakeholders, termed 'recipients' within I-PARIHS, was a central feature of PRESCRIBE, with 6 key groups of recipients included. Representation extended from lay CYP in the school setting to those with experience of emergency and critical care services (CYP and parents) as well as health and research personnel. In total 240 participants contributed to PRESCRIBE, including 146 CYP, through both quantitative and qualitative methods. PRESCRIBE has therefore achieved representation from relevant personnel and established that service users, health and research personnel value medicines' optimisation and appreciate the importance of PK research.

In the sections below the barriers and facilitators associated with core themes are reviewed for similarities and differences between the recipient groups and in relation to the evidence from the scoping review.

9.2.2.1 Recipient responses compared by the number and distribution of comments

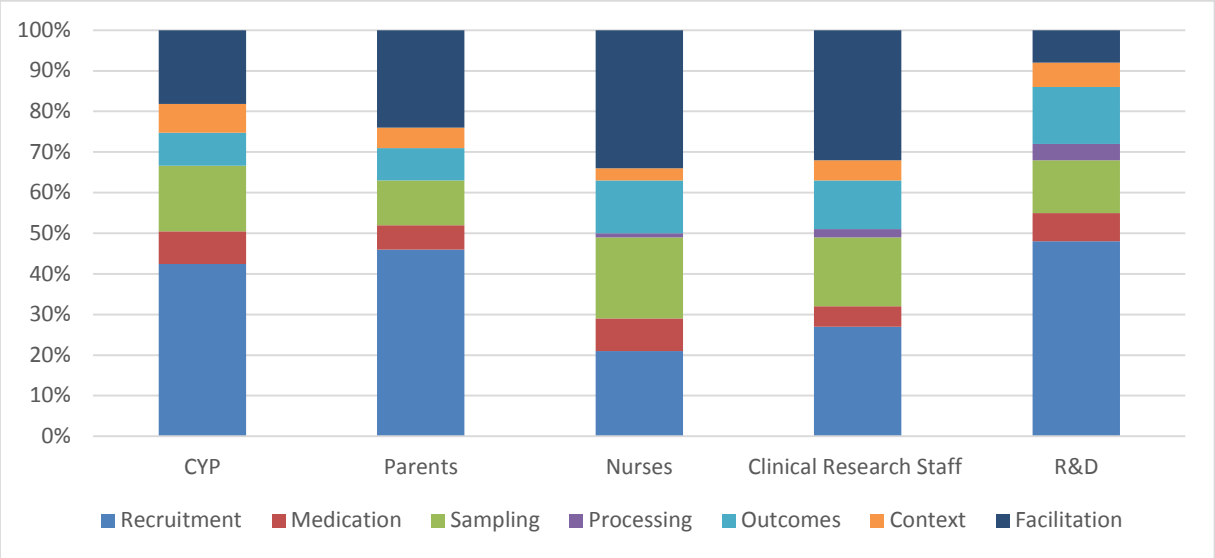
The five participant groups had their responses coded to seven core themes, although the individual sub-themes varied for each group. *Table 63* shows the number of comments per theme for each participant group as well as the total number of comments / group. There was large variation, with only 424 coded comments from R&D staff compared to 3169 comments by CRN staff however this appears to be in keeping with the total number of participants per group (see column 2).

Table 63: the number of comments per theme for each participant group in PRESCRIBE

	No. participants	Recruitment	Medication	Sampling	Processing	Outcome	Context	Facilitation	Total
CYP	**26**	628	116	245	1	118	107	271	**1486**
Parents	**18**	1041	130	251	8	178	116	547	**2271**
Nurses	**29**	275	98	259	13	161	34	441	**1281**
CRN	**43**	863	165	534	59	375	154	1019	**3169**
R&D	**4**	203	28	54	17	61	26	35	**424**

Using a stacked column chart (see *Figure 64* below), the breakdown of how much each theme was discussed by each group is shown.

Figure 64: participant group comments per theme (% of total number of comments made)



Recruitment was a significant topic across participant groups. However, this was a priority area for discussion amongst CYP, parents and R&D staff, with 42%, 46% and 48% of their comments (respectively) coded to recruitment. Nurses and CRN staff, by comparison made fewer comments overall on this topic (21% and 27% of their total comments), although there were still large numbers of comments from CRN staff (843). Comments focused on medications, processing and outcomes were relatively consistent in number across participants groups. Nurses and CRN made a large number of comments about sampling, 20% and 17% respectively of their total comments were coded to aspects related to sampling. They also commented about factors that facilitated PK research (34% and 32% respectively of comments). R&D staff commented less overall than any other group. They also commented the least on facilitative factors, which fits with observations made about their slightly submissive approach. However, they were also the smallest group (n=4).

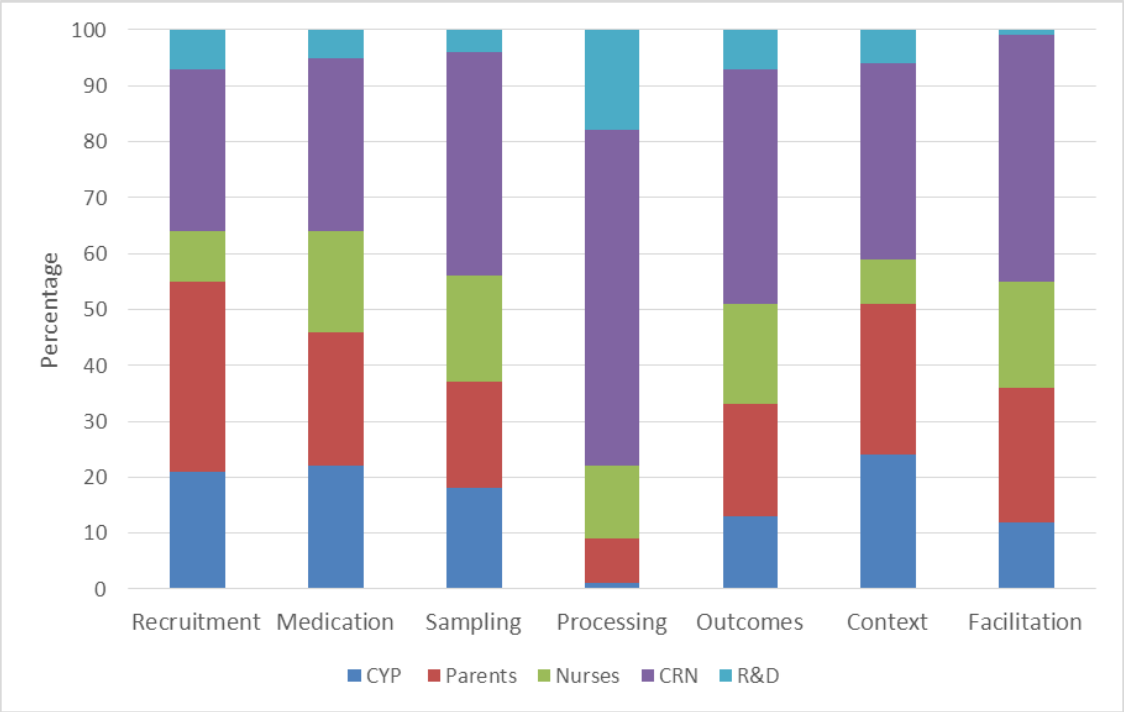
9.2.3.2. Recipient responses reviewed by theme

Each theme was also examined to allow review of contribution on a topic (see *Table 64* below). Using a stacked column chart (see *Figure 65* below) the breakdown of how much each group contributed to discussion on each theme is shown.

Table 64: comparison of all coded comments per theme by participant group (percentage)

	Recruitment	Medication	Sampling	Processing	Outcome	Context	Facilitation
CYP	628 (21%)	116(22%)	245(18%)	1(1%)	118(13%)	107(24%)	271(12%)
Parents	1041 (34%)	130 (24%)	251(19%)	8(8%)	178(20%)	116(27%)	547(24%)
Nurses	275(9%)	98 (18%)	259(19%)	13(13%)	161(18%)	34(8%)	441(19%)
CRN	863 (27%)	165 (31%)	534(40%)	59(60%)	375(42%)	154(35%)	1019(44%)
R&D	203 (9%)	28 (5%)	54(4%)	17(18%)	61(7%)	26(6%)	35(1%)
Total	**3010 (100%)**	**537(100%)**	**1343(100%)**	**98(100%)**	**893(100%)**	**437(100%)**	**2313(100%)**
Range	9-34%	5-31%	4-40%	1-60%	7-42%	6-35%	1-44%

Figure 65: number of comments per theme (%) (by participant group)



Contributions within themes were relatively consistent across participant groups for medication, sampling and outcomes. R&D staff provided very low volumes of comments on all themes, apart from processing where they contributed 60% of the comments made. CRN

staff made the largest contribution to all themes, reflecting the number of participants in this group (n=43) but also perhaps reflecting their expertise in research. The exception was recruitment where 55% of the total number of comments came from CYP and parents, highlighting the importance of these topics to service users.

In conclusion quantifying the comments by both the theme and the participant group helped triangulate the qualitative themes expressed and discussed by participants (Sandelowski, 2000a, Moule and Hek, 2011, Parahoo, 2014). Priority areas for CYP and parents were recruitment and context, nurses and CRN staff made the most comments on sampling and facilitation (although CRN staff spoke in volume on all aspects) and R&D staff were generally focused on recruitment, although with a different focus to other groups. Barriers and facilitators from the scoping review and recipients' perspectives (chapters 3,5,6,7 and 8) have been compiled in *Table 65.*

Table 65: summary of barriers & facilitators (from chapter 3,5,6,7,8)

Theme	Sub-theme	Perceived barriers	Perceived facilitators
Recruitment	'Vulnerable' participants'/ families	Infants Palliative patients Age of CYP (barrier & facilitator) Acuity of condition / situation	Choice / opportunity Personal benefit Help others Age of CYP (barrier & facilitator) Levels made available for care No additional samples/ sampling procedures Deferred consent (emergency situations)
	Communication / comprehension difficulties	CYP incapacitated /additional needs Parental distress	Preparation Communication Involve CYP Support joint decision-making
	Pain / distress	Additional painful procedures Blood sampling Negative past experiences	Analgesia Distraction techniques Use of indwelling lines
	Appointments	'Extra' appointments Missing school Missing work Additional travel	Joint clinical / research appointments Flexibility with appointments Home visits
	'Experimentation'	Trials of 'routine' medications Trials of innovative medications Uncertainty Perceived lack of choice	Personal benefit Help others
	Safety	Patient / family concern Health professional concern	Reference to guidelines Visible engagement clinical & research teams Education / training
	Organisational	Insufficient funding Unfeasible / no capacity Unrealistic targets	Feasibility review at local level Capacity review Realistic targets set
Medication	Accuracy	Errors in preparation / administration Study requirements	Research support Training Trial documentation

Theme	Sub-theme	Perceived barriers	Perceived facilitators
	Formulation	Tablets Palatability Formulation issues	PPI Pharmacist review
Sampling	Vascular access	Additional cannula Capillary sampling Additional access to CVL / Arterial lines	Avoid cannulas/ capillary samples Use indwelling vascular access
	Blood volume Frequency	Anaemia Patient stability Safety	Reference to guidelines Engagement with clinical teams Consider population PK approaches- opportunistic sampling, scavenged samples, non-blood
	Regime	Infection risk Disturbing Precision	Training Support from senior staff/ research team
Processing	Accuracy	Inaccuracy in documentation Technical failure	Training Trial-related documentation Involvement of lab staff
	Storage / transportation	Incorrect storage / transportation	Clear guidelines Adequate staffing resources (Labs / CRN)
Outcomes	Clinical nurse workload	Excessive nurse workload Lack of senior nurse support Clinical prioritisation	Engage with clinical staff Senior clinical staff support Plan for 'out of hours'
	Research staffing resources	Research staff unavailability 'Unsocial hours' cover	Embedded research team Outreach research support
	Organisational	Negative research culture	Feedback results of research to staff Research culture
Context	Ward areas	Lack of research infrastructure	Use designated research facilities (outpatient) Use PIC (if an inpatient) Ward- ensure adequate staffing (clinical & research)

9.2.2.3 Barriers and facilitators by theme

9.2.2.3.1 Recruitment: summary

Despite the scoping review reported in Chapter 3 going back to 1990 only 38 papers were identified which reported recruitment rates to paediatric pharmacokinetic studies. Only seven of these papers provided rationale for why participants and their families declined participation (Carlsson et al., 1997, Agertoft et al., 1999, Conway et al., 2004, Dupuis et al., 2006, Kokki et al., 2006, McGregor et al., 2012, Altcheh et al., 2014). Rationale focused on the requirements for additional blood sampling and additional hospital visits. The qualitative work undertaken in chapters 5-8 therefore adds significantly to what is known about barriers to recruitment. This includes perspectives about those deemed 'vulnerable', as well as the influence of the CYP health status at the time of approach, the acuity of the situation, negative past experiences, the type of trial and nature of the medication being offered, wider impact of attendance on CYP and parents as well as organisational considerations such as departmental capacity and targets. Overall the groups were similar in their recognition of barriers. The key difference was the impact of extra appointments on families was under estimated by health and research staff. R&D staff emphasised the barriers of funding, capacity and unrealistic targets, rather than aspects specifically related to study design or participants.

The scoping review identified no studies which featured strategies to promote recruitment to PK trials, however all participant groups contributed valuable observations about facilitation. The groups were similar in being positive about the importance of an inclusive approach to recruitment, the importance of good communication and a sensitive approach and there was support for the use of a deferred consent model in time sensitive / emergency situations, which is consistent with the published literature (Morris et al., 2004,

Morris et al., 2006, Harron et al., 2015). There was also agreement that additional research appointments should be avoided, or coordinated with clinical care and flexibility in times of day / day of the week offered. The importance of being involved in decision-making was one of the most highlighted factors by CYP, both in the lay population and by those with health care experience, a finding supported by a recent study with adolescents (Ingersgaard et al., 2017). The strength of CYP desire to be involved in the process was however underestimated by clinical and research staff and even parents. Research personnel also underestimated the positive influence of altruism on decision-making for service users, emphasising instead the influence of personal benefit. Research staff need to ensure they are aligned with the perspectives of service users when designing and conducting research or risk poor recruitment and retention. Unless future studies are designed with service users' preferences or utilise strategies identified as facilitating there is a risk that high declining rates of 41% and over will be perpetuated.

9.2.2.3.2 Medication: summary

CYP wtithin paediatric inpatient settings and particularly within the PIC setting are vulnerable to medication errors (Manias et al., 2013). The scoping review identified this situation can also occur in the context of a clinical trial and can result in the withdrawal of participants and their data from trial analysis. The issue of prescription or administration errors within research was not specifically reported within the qualitative work. However health and research personnel did make references to the challenges of timeliness and accuracy. The scoping review also identified problems related to adherence to the medication regime or problems associated with the trial formulation which were coroborated by service users, health and research personnel.

Nursing staff were the only group to discuss potential solutions to issues with medication delivery. They emphasised the value of effective study documentation to promote accuracy, training on adherence to the trial protocol and adequate research support to assist with trial medication preparation and administration. In keeping with a published study about the role of pharmacists (Girard et al., 2013), R&D staff suggested the early involvement of pharmacy staff to review and anticipate any issues associated with drug availability and formulation. They also highlighted the value of PPI to review CYP and parents' priorities, views and preferences. This was also emphasised by CYP and parents who stated the importance of ensuring the acceptability of study tablets and formulations prior to commencing a trial. PRESCRIBE participants were all aware of problems surrounding the medicine management of CYP. To minimise issues within a PK trial these must be considered early on in the design stage.

9.2.2.3.3 Sampling: summary

The scoping review identified that sampling issues from infants and children were the most reported problem within the published PK literature (n=112 studies). These reflected studies which had experienced problems obtaining complete samples, missing samples or incorrect sampling. This caused the loss of approximately 10% of patients' data, although there were examples of studies which had lost 80% of data (Woloszczuk-Gebicka et al., 2014). This was corroborated through the qualitative work. All participant groups were negative about capillary samples or sampling from a cannula, the frequency of sampling and were concerned about the safety of blood volumes and the specificity of study protocols; although there was some variance between groups on which were the most problematic issues.

Numerous facilitators were identified. Some worked to provide reassurance or personal benefit to families and health care professionals through reference to guidelines on acceptable blood sampling requirements, discussion about the individual patient between research and clinical staff or feedback of research findings to inform clinical management. Other facilitators fitted with strategies that reduced the emotional stress associated with sampling through the use of analgesia and distraction techniques. Strategies to overcome the practical challenges of additional blood samples involved methods that informed a population PK approach, such as opportunistic sampling and scavenged samples; these were highly rated by families, health and research staff. Studies which continue to utilise traditional PK approaches with high volume, high frequency sampling run the risk of failing to recruit or retain participants or failing to adhere to the protocol, with the subsequent risk of missing or inaccurate data..

9.2.2.3.4 Processing: summary

Inaccuracies in documentation of sampling can impact on the processing and interpreting of samples. This problem contributed to the loss of approximately 5% of participants' data within the scoping review (n=16 studies). This is correlated with comments from parents, nurses, CRN and R&D staff over the accuracy of sampling documentation. The scoping review also identified problems associated with technical aspects which related to the mishandling of samples as well as storage and transportation issues, aspects not widely reported on by participants in the qualitative work. This issue is perhaps more significant than consumer, health and research personnel perceived, possibly because the issue is only recognised on analysis which may take place several months or years after samples were taken. Trial-related documentation and associated training were identified as the biggest facilitators to target accuracy. However, staffing resources to ensure sample handling,

storage and transportation are essential. This is a concern at a time when R&D staff identified budget cuts to areas such as laboratories. These must be considerations within the assessment of future PK trial capacity.

9.2.2.3.5 Outcomes: summary

Withdrawal of consent or loss to follow up were significant issues within the scoping review (n=43 papers), causing the loss of a median 8% of participants. Reasons for withdrawal (n=15/43 papers) reflected extra blood tests and extra hospital appointments. Withdrawal was not identified as an issue within the qualitative work and so does not specifically feature as a barrier. However, this does mean that conclusions drawn about influences on recruitment can also logically be applied to influences on study withdrawal or attrition.

The key barrier to the success of a study participant having all the data collected at all the correct time points were the resources available to support the study. Although clinical staff were well-placed to support research activity, all PRESCRIBE participants identified that they experienced a heavy workload and would struggle with prioritisation and responsibility for research requirements. There were also felt to be issues associated with the availability of research staff as the role has traditionally assumed a Monday-Friday, office hours basis. The culture of the organisation towards research was also widely acknowledged to be influential on the attitudes of patients, families and staff towards research; if this was negative then conduct would be challenging. Despite these barriers, there was a strong sense of support for PK research with 82% of CYP, 94% parents, 100% nurses, 98% CRN and 75% R&D staff stating they would participate in or support a PK trial. This is significantly higher than figures calculated within the scoping review of 59%, however as the qualitative study was posed on a hypothetical basis it is likely consent rates would in reality be lower. Consent rates from lay CYP were closer to the scoping review, with only

49% saying 'Yes' to participation, although only 19% would say No outright. Overall the key facilitator for successful outcomes was appropriate research support. Where the groups differed was that CYP and parents were less opinionated on where this support came from. Health and research staff however, emphasised the value of department specific research teams, operating on a minimum of 12 hours / day, 7 days a week basis.

9.2.3 Context

9.2.3.1 Local context

The context is an integral part of all determinant frameworks (Nilsen, 2015) and is well-recognised as an influential factor on the success of an implementation (Kitson et al., 1998a, Kitson et al., 1998b). The influence of where the research takes place was not a well-reported factor within the papers included within the scoping review. However, context was identified as extremely influential by qualitative participants (n=120). Neither service users, health or research personnel had confidence in PK research being well-conducted in ward areas. Designated research facilities were favourably viewed, but best suited to those classed as outpatients. PIC as a location for research was viewed positively by all participants due to the presence of intravascular devices, analgesia and the high staff to patient ratios. However, PIC nurses had concerns about the acuity of patients and their ability to adhere to a PK protocol, despite the 1:1 ratio. All participant groups were concerned about the workload of clinical staff and expressed concerns about the impact for trial conduct if staff were not adequately supported.

9.2.3.2 Organisational context

Whether research is delivered by a department specific or outreach service, nursing and CRN staff would like to see funded support for around 60% of the time, 7 days / week. The preference is for this to be a locally based competent research team who are familiar with the clinical environment, rather than a generic outreach model. It is also worth noting that

outreach teams are also wary of environments such as PIC and can be reluctant or unable to take an active role in research activities such as sampling. At an organisational level, this requires strategic planning to ensure there is capacity to support approved studies and the refusal of studies which are not adequately funded. The organisation also needs to devise a strategy for coordinating research and routine clinic appointments. With recognition that additional appointments are unacceptable to CYP and parents, there is a requirement to formalise coordinated services as a research strategy. The organisation also has a responsibility to consider the development and sustainment of a research culture, with better preparation for families about on-going research, the provision of feedback from research and the use of social media to highlight the place of research.

9.2.3.3 External health care context

The outer context reflects the wider health care system and the influence of policy, regulatory and political infrastructures (Harvey and Kitson, 2016). Emerging themes from PRESCRIBE reflected work to be conducted at a national level, to cultivate the research culture and the acceptability of being approached, similar to the organ donation movement. There are also recommendations from the NIHR to improve the education to CYP about the purpose and conduct of research (National Institute for Health Research and GenerationR., 2014, National Institute for Health Research, 2015c). This would lead to improved knowledge and understanding of the public about the research and potentially increase engagement. From a policy perspective, many of the research staff worked for NIHR CRN research networks which provide research infrastructure and support across departments and institutions. However, participants within PRESCRIBE emphasised a preference for embedded research staff within specific departments, which is at odds with the local and national research strategy. Findings from the scoping review highlight a need for a change

in culture towards the reporting of PK studies. Studies should be reported to the same standard as other studies with accuracy and transparency in reporting research (Simera and Altman, 2009).

The influence of context on the conduct of PK research has not previously been reported. PRESCRIBE highlights issues at local, organisational and national level that influence the conduct of quality PK research. These principles were derived from consideration of PK research studies but could be relevant to the set up and conduct of other paediatric research studies.

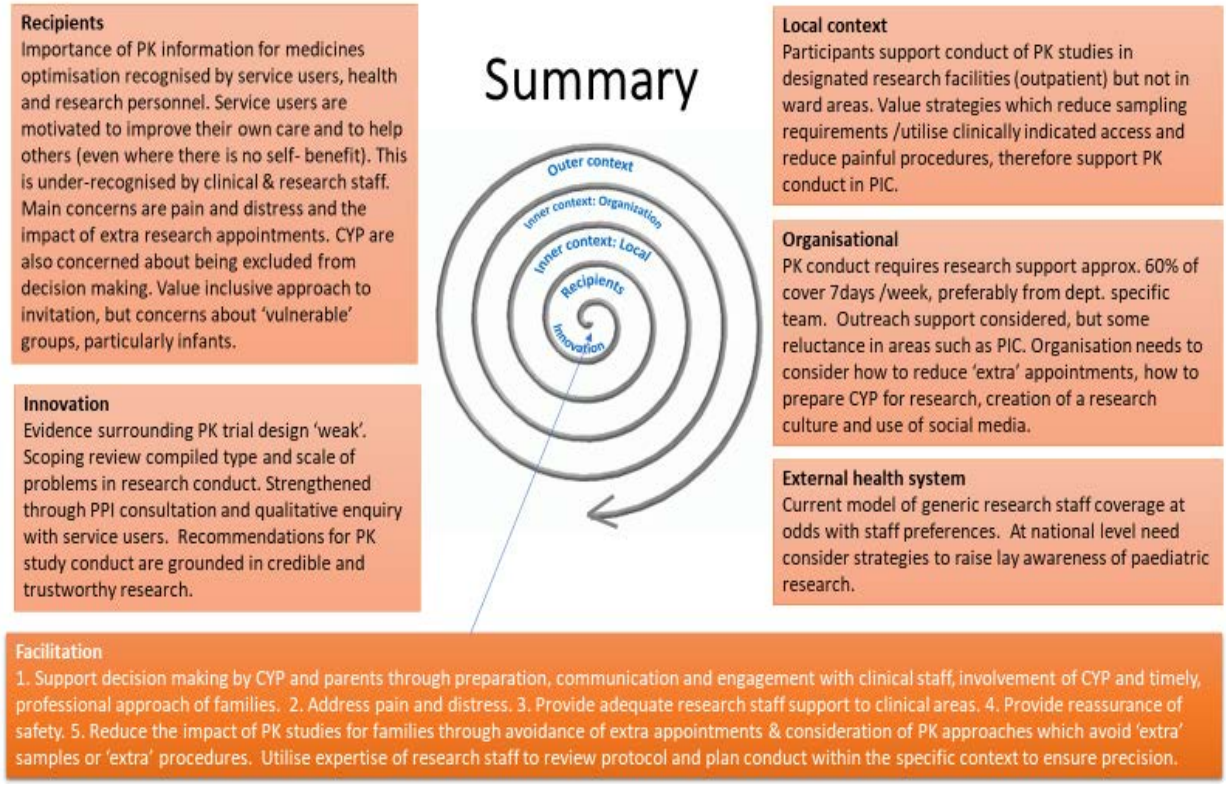
9.2.4 Facilitation

Throughout the study facilitators have been identified. From these a simple facilitation model has been developed (see *Figure 66* below), recognising that some aspects were applicable within several themes.

Figure 66: summary of facilitation (from all participant groups)

All the findings from chapters 3-8, have been plotted into a summary I-PARIHS diagram (see *Figure 67* below).

Figure 67: I-PARIHS summary of PRESCRIBE



9.3 Reflexivity

As outlined in Chapter one, there were a number of influences on the author, JCM during the conduct of the project. Being a nurse with experience of PIC, the lead nurse for the PIC research nursing team and a former research nurse within the NIHR networks offered useful insights, however it also involved juggling role demands or expected responses. This challenge of managing blurred role boundaries is recognised as a particular challenge within nursing (Gerrish, 2003). Over time strategies and scripts developed to assist with managing these situations and supervision was used as a time to reflect on these situations. During the conduct of the PhD the researcher also became a parent to two children, both of whom were service users at a (different) children's hospital and were themselves research

participants. Being on the 'other end' of health and research care provided personal insight into decision-making about research, particularly decision-making for a previously fit and healthy child in an acute and time limited situation. Ultimately these experiences helped with understanding participants' perspectives whilst reflection and carefully documented audit trail helped to ensure transparency at all stages.

9.4 Limitations to PRESCRIBE

9.4.1 Pilot project

The study as originally outlined, was going to culminate in a small pilot of a PK study of a medication, using the evidence gained to design the study protocol. However, with little existing knowledge on which to base this pilot, there was a rapid realisation that this would not be achievable within the timeframes of the project. Instead the focus changed to gathering the highest quality data on which to base recommendations for PK conduct. Whilst this means that the recommendations generated have not been implemented into practice, the researcher is confident that they are grounded in evidence. There are clear audit trials demonstrating the decision-making process and data is tracked to sources to emphasise the confirmability and credibility of themes and sub-themes (Lincoln and Guba, 1985). Simultaneous data triangulation of the five qualitative work-streams allowed constant comparison between participants of the same group and between participant groups (Sandelowski, 2000a, Moule and Hek, 2011, Parahoo, 2014). This facilitated the exploration of similarities and also highlighted negative cases (Parahoo, 2014). The recommendations are therefore felt to be grounded in credible and trustworthy analysis.

9.4.2 Subject areas

Since the study was started in 2010, innovations within the field of pharmacokinetics have emerged or developed; such as methods for obtaining blood specimens by participants themselves 'self-sampling' (Leichtle et al., 2010), other alternatives to blood, urine and saliva such as analysis of hair samples (Roberts et al., 2015), the use of dried blood samples (Patel et al., 2010, Patel et al., 2013) as well as developments in pharmacometrics and pharmacokinetic pharmacodynamic modelling (Coppini et al., 2016, Standing, 2016). It was not possible to review the acceptability and feasibility of all specific methods, however many avenues were reviewed and comparison across service user and health care professional participants was possible.

9.4.3 The duration of the study

The PhD funding was awarded in 2009 when research into children's medicines was a high priority (Saint-Raymond and Seigneuret, 2005, Duffin, 2007, Sammons and Choonara, 2007, Choonara and Bauchner, 2008). There were concerns whether eight years on in 2017 the results from PRESCRIBE would still be relevant. However, the answer appears to be yes. The research climate and culture across the NHS is improving (Department of Health, 2015). Children and young people are recognised as one of the 30 core research specialities (National Institute for Health Research, 2017) and the number of participants recruited annually to NIHR CRN studies has increased ten-fold (Lythgoe et al., 2017). Medicines research is benefiting from advancing techniques to conduct early phase drug studies in children and Rieder and Hawcutt (2016) assert that there has never been a better time for conducting drug studies in children. Paediatric patients are exposed to substantial polypharmacy and are at risk of drug-drug interactions, particularly those with rare diseases (Feudtner et al., 2012). Knowledge of clinical pharmacology, pharmacokinetics and

pharmacodynamics to personalise a patient's treatment is essential for the future (Bhatt-Mehta, 2016). The value of this work, which was recognised in 2009, therefore remains valid in 2017. The output from PRESCRIBE will help inform future PK research studies, not only within PIC but across paediatric settings.

9.5 Future research

9.5.1 Improvements in PK reporting

One of the key findings from the scoping review was the lack of standardisation of reporting across published pharmacokinetic studies. Complete, accurate and transparent reporting should be regarded as an integral part of good research and publication practice (Simera and Altman, 2009) and this review highlights that reporting within this field of health care research is currently inadequate. Recommendations for pharmacokinetic research reporting have recently been developed through expert consensus (Kanji et al., 2015) and these are registered on the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) website (EQUATOR Network, 2017). Whilst this is an important step forward to improving the accuracy and transparency of publications, there is no evidence yet of the impact of these on reporting. In addition, this work was conducted without qualitative consultation with service users and health professionals. Further examination is therefore required to ensure this captures all of the findings from PRESCRIBE.

9.5.2 Patient and public involvement and engagement

One of the most difficult aspects of the whole PhD project was trying to undertake PPI with parents with relevant experience. The challenges of this experience led to the paper Menzies et al (2016). PIC is a complex and expensive area with many types of service user, patient acuity and outcome. Research in this area is challenging and researchers need to ensure that the public are engaged to ensure that future research is well designed and

acceptable to patients and their families. Moving on from this, national collaboration is required with discussions of how PIC clinicians and researchers as a whole undertake meaningful PI with this difficult-to-reach group.

9.5.3 CYP and parents

Conducting research with lay CYP within the school setting and those with experience of the hospital setting was challenging but rewarding. Neither group is well represented within published research and future research must make efforts to engage directly with CYP who can participate if the right method and support is found (INVOLVE, 2016a, INVOLVE, 2016b). In the school setting, there would be value in distributing the questionnaire on a wider basis, to more schools and allow a wider perspective and enhance the transferability of results. In addition, the study could be extended to those in year 8 and below to explore developing attitudes and views and allow further comparison across secondary school. Research with CYP with experience of hospital and participation in research has often focused on those with specific diseases, notably cancer. There are no accounts the researcher is aware of about those who have participated in research within the PIC setting. This is particularly important given the emphasis CYP themselves placed on wanting to participate in decisions about consent, which is challenging in the face of acute illness or trauma. Future research could also extend beyond a single PIC to a multi-centre study and review the transferability of research findings to another setting (Moule and Goodman, 2009).

Parents were the hardest group of participants to engage with. Reasons for this were attributed to the complex needs of their children and the responsibilities they have for care delivery, even within the hospital location. To overcome some of these the researcher

conducted 7 interviews (8 people) within the parent's own home. Future research could explore parents' preferences using alternative methods of engagement such as on-line forums, on-line surveys and interviews via video-conference calling (VIPER, 2013, National Institute for Health Research and GenerationR., 2014, INVOLVE, 2016b). These methods might facilitate participation from people who otherwise might not have the time, energy or transportation means (Menzies et al., 2016). Recruitment and attrition are known problems to the conduct of research (Shilling et al., 2011, Tishler and Reiss, 2011) and the identification of methods to increase accessibility and facilitate participation is vital to address these.

9.5.4 Health and research personnel

PRESCRIBE features 26 PIC nurses and 3 staff from high dependency wards. In order to draw more conclusions a possibility is to extend recruitment to another PIC. There are variations in acuity and speciality amongst PICs and staff in a different hospital might have different views about PK research conduct. In addition, extending the work to more ward staff would offer more insight.

Representatives from two NIHR paediatric networks participated with PRESCRIBE. In order to explore CRN staff attitudes on a wider scale there is the possibility of extending the work across the NIHR paediatric network. Large sums of money are invested within the NHS Research infrastructure to support the conduct of research studies. However, the findings from PRESCRIBE suggest that the current model is not optimal for the conduct of PK studies. Further debate could be enhanced by an exploration of the cost implications for different service models and heath economics evaluation. In addition, further research could focus on evaluation and comparison of service users' experiences to explore consumer preferences further.

It would also be interesting to conduct further work to explore the approvals processes further, both at local R&D level and also within the REC approval process. With significant re-configuration to the research approvals process over the last two years, it would be interesting to review staff attitudes and perspectives on the challenges of decision-making now.

9.5.5 Guideline development

With draft recommendations now developed (see Chapter 10), the next stage is to obtain external review with experts within the pharmacology field. A recent study on deferred consent in trials of emergency treatment of critically ill children (CONNECT Advisory Group, 2015, Woolfall et al., 2015a) developed their study findings into recommendations through a one day guideline development meeting (Lyttle et al., 2014). The plan is therefore to develop a working group to develop these guidelines further using expertise from the PK field. This work will be conducted later in 2018 following on from the PhD submission.

9.6 Conclusions

In 2009 at the time the scholarship was awarded there was wide spread recognition that it was unacceptable to continue to use medications off label and off-license, particularly in the most vulnerable patient groups (Conroy et al., 1999, Conroy et al., 2000). Very little qualitative research concerning research design had taken place, despite the fact that researchers acknowledged paediatric research to be challenging (Caldwell et al., 2004). Within the field of pharmacokinetic research, barriers to recruitment and trial conduct are alluded to in the published literature (Anderson et al 2007), but the scale and magnitude of problems or the identification of solutions had never been classified. Utilising principles of implementation science, PRESCRIBE has compiled evidence from a mixed methods approach, including a scoping review, public consultation and qualitative inquiry with 240

participants into stakeholders' attitudes and perspectives, with the overall aim to explore acceptability and design of PK studies in paediatrics. Importantly the work has established that the conduct of PK research is viewed as important by both service users and health professionals, with both groups recognising the importance of optimisation of medications. The biggest barriers to the conduct of PK research were found to be the requirement for blood sampling and additional painful procedures, additional 'research' appointments and the lack of resources to conduct PK research within inpatient facilities. To address these, researchers must take action to ensure pain and distress are minimised, additional clinic appointments are avoided or minimised and there is sufficient support by trained research personnel. Despite concerns about the timing and approach of families, the conduct of PK research within PIC was regarded by service users and health professionals as acceptable, due to the presence of intravascular access, analgesia and good staff: patient ratios. This is an important finding as patients within PIC have been identified as those most in need of studies for both efficacy and safety. The output from all of this work is evidence-based recommendations to assist future researchers with future research conduct. It is envisaged that better designed studies which are more acceptable to CYP and their families as well as to the clinicians who implement them, will facilitate studies which recruit to target with minimum attrition.

Not only does research design need to improve to reflect the concerns of service users and health professionals, but so does the quality of reporting about the conduct of PK studies. It is unacceptable to ask patients and their families to participate in poorly designed PK studies which then fail to adequately report all stages of the patient journey, fail to report problems encountered in research conduct and fail to highlight significant design flaws to future researchers. Inadequate reporting hampers assessment of a study's strengths,

weaknesses and generalisability (Von Elm et al., 2007). Standards have recently been published to improve this situation (Kanji et al., 2015). The impact of these has yet to be examined but it is hoped these will improve the transparency of PK research and overall will result in improved quality conduct and reporting of PK studies.

Chapter 10: Recommendations for PK study conduct

10.1 Introduction

Recommendations have been generated from the work conducted throughout PRESCRIBE as detailed in chapter 2-7. Items were coded to 'recommendations'- some generic and some very specific statements- and then compiled using the same themes utilised throughout the study. An additional category was created: 'study set up' reflecting factors that needed to be identified and dealt with before a study should open to recruitment. See *Figure 68* below.

Figure 68: 'new' category 'study set up' added

The source(s) of evidence for the recommendations are coded alongside each point using the initials identified in *Table 66* below.

Table 66: summary of how recommendations were compiled from chapters

Chapter	Method
Chapter 3: scoping review (SR)[1]	• Reviewed themes and sub-themes • Review papers identified during search reviewed (as additional reference material)
Chapter 5: survey with school children (SC)[1]	• Questionnaire responses reviewed • Free text responses reviewed
Chapter 6: qualitative descriptive study with Children (CYP)[1] & parents (P)[1]	• NVivo 11: node created 'recommendations'

Chapter	Method
Chapter 7: qualitative descriptive study with nurses (N)[1]	• If there was an element of advice or caution material was also coded to recommendations (in addition to themes) • All coded material reviewed and added to themed recommendations
Chapter 8: qualitative descriptive study with Clinical Research Nurses (CRN)[1] and R&D staff (R&D)[1]	

[1]Abbreviations used in the recommendations below

Where evidence was generated from multiple chapters, multiple codes are identified and where there is additional reference material to support this this is also indicated as a referenced source.

The approach taken is in keeping with that of a post-doctoral paediatric research project to explore parent and research personnel views on consent in children's critical care trials (Woolfall et al., 2015b). The study utilised a similar mixed methods approach of surveys, interviews and focus groups and achieved recruitment of 23 parents (interview), 10 research nurses, 3 Doctors, 4 clinical trials research staff (focus groups) as well as 275 parents (questionnaire). From PRESCRIBE there is survey data from 120 school children, focus groups and interviews with 28 CYP, 18 parents, 29 nurses, 43 Clinical Research Staff and 4 R&D staff as well as findings from 203 published PK papers summarised within the scoping survey. This is felt to be a representative group from which to draw recommendations and the next step is to develop the recommendations further, using a similar approach to CONNECT of expert consultation and consensus (Lyttle et al., 2014).

10.2 What type of trials are these recommendations useful for?

This guidance has been developed for any study that features PK sampling within any topic area within paediatrics. The principles cover all research designs, although it is recognised that there are more restrictions in place within Phase I and Phase II studies. Although the

recommendations have been developed to guide those involved in PK studies, they may be of use for the design and conduct of other studies within paediatrics that involve biological sampling. Recruitment to clinical trials with CYP has been said to be the one of the biggest challenges for researchers to overcome (Caldwell et al., 2004, Sammons et al., 2007a), particularly within the PIC setting (Kanthimathinathan and Scholefield, 2014). Therefore, practical guidance which reduces demand and burden on families may be of use. This guidance features advice which is in line with GCP guidelines (National Institute for Health Research, 2016a), but is not designed to replace them as these are a legislative requirement (Department of Health, 2005).

10.3 Who are these recommendations written for?

This guidance is for all those who have a role in the design and conduct of paediatric or neonatal trials that involve PK or blood sampling. This may include Doctors, Nurses and Research Staff with a role to play in conducting research studies. Those with a role in reviewing and approving research such as Patient and Public Involvement (PPI) representatives, members of NHS Research Ethics Committees (RECs) and Research & Development teams may also find this information useful. It is anticipated these guidelines will be of interest to those who are involved in the design of research within Clinical Trials Units, Pharmaceutical companies and those who fund research studies.

10.4 Recommendations

Section 1: Study set up

Section 1: study set up
Recommendation 1.1: Hospitals need to raise awareness that a hospital is research active
• There needs to be a clear message that a hospital conducts research and that parents can expect to be approached about research if their child is eligible for a study (P, CRN) • The message about research taking place needs to be reinforced through letters or information sent through with clinic appointments and correspondence from the Hospital, recognising research can occur at any stage of a patient journey (P, CRN)
Recommendation 1.2: Preparation for CYP and families about PK research should take place as early as possible
• Inform and prepare patients and their families wherever possible, about studies which are in set up or actively recruiting (P, CRN) • Written information sent out prior to hospital attendance will allow CYP and parents a chance to familiarise themselves with a PK research study. This could extend from receiving information the day before a child's operation to receiving information during the antenatal period if this is appropriate to the study (SC, CYP, P, CRN) • Consider making information about trials such as posters or leaflets available in areas where families might see them, such as coffee rooms and waiting areas (CYP, P, CRN) • Clinical staff should be adequately prepared with information about the study so they are facilitated to answer questions during this information-giving phase (P, N, CRN)
Recommendations 1.3: Planning and organisation is crucial to PK study set up
• The researcher and / or research staff[2] will be familiar with the protocol and conduct a thorough review of the feasibility of all stages at the local site (CRN, R&D) • There needs to be a period of education and training for clinical staff about the study, the aims and what the impact will be for clinical care (N, CRN) • A key aspect of the study launch is to identify key tasks with clear definition of who

[2] There are many different job titles used within research literature. For continuity Research staff is used to represent 'research nurses', 'research facilitators', 'trial managers': all members of research staff who have a role to play in research study conduct and who have patient contact.

Section 1: study set up

will undertake each aspect (N, CRN, R&D)

- Precision is a key element of PK studies and research staff will take responsibility for developing tools to facilitate accuracy in relation to both medication administration and accuracy in sample collection (N, CRN, R&D)
- There should be a clear outline of the research support clinical staff can expect to receive and how to access it (CYP, P, N, CRN, R&D)
- Where possible plan the study so there is a personal benefit to participation for CYP or parents, such as extra monitoring or extra clinical review (P, CRN)
- Where there is no personal benefit to participation avoid unnecessary additional visits and / or procedures and highlight clearly what the benefits of the research are for other CYP and parents (P, CRN)

Recommendation 1.4: Consider the model of consent, particularly for studies with a time-sensitive element or in a challenging environment

- Researchers could consider a model of 'pre-consent', where CYP and parents' consent in advance and then consent is re-affirmed on the day of the trial commencing (N,CRN) (Macrae et al., 2014)
- Deferred consent or 'research without prior consent' (Morris et al., 2006, Harron et al., 2015) could be considered if a PK study is targeting patients in the acute stages of an illness (CYP, P, N, CRN)
- When samples are taken there should be some form of acknowledgement that samples are being taken and their consent will be sought at a later stage (P, N, CRN)

Recommendation 1.5: Consider the use of social media as a resource for PK studies for CYP and parents

- CYP and parents use social media for advice or support about clinical care and there is a suggestion this could extend to research studies, including PK studies (P)
- Consider development of an on-line resource highlighting study participant's experiences of participation within a PK study (P)

Recommendation 1.6: Participant Information Sheet (PIS) need to be presented in a simple, clear format

- The PIS needs to be written clearly and in a straightforward manner, explaining clearly what the study involves, particularly if there is a change in study medication involved (P, CRN)

Section 1: study set up

- Consider recording the PIS in a different format, such as a video which can be watched or listened to on multiple occasions and facilitate understanding (P)

Recommendation 1.7: Ensure the PK study has sufficient resources for successful recruitment

- Appropriately trained research staff are a key factor in the successful conduct of PK studies. Funding must provide adequate staffing resources. (CRN, R&D)
- Realistic recruitment targets need to be set which reflect recruitment rates for PK studies (CRN, R&D)
- Researchers need to build in monitoring of study withdrawal and attrition. This will facilitate early review of problems and allow for timely amendments (CRN, R&D)

Section 2: Recruitment

Section 2: Recruitment

Recommendation 2.1: Recruitment by clinicians and researchers should be inclusive and transparent

- Clinicians and researchers should offer CYP of all ages and parents who are eligible for PK studies a choice about participation in PK studies, respecting their right to autonomy (CYP, P, N, CRN, R&D)
- PK study recruitment should be transparent with reporting showing clearly who was invited to participate, rates of decline and clear participant flow throughout the study in the same manner as CONSORT guidelines (SR) (Schulz et al., 2010)
- Non-invitation is not supported by CYP and parents, provided there is sensitivity in the manner and timing of approach invitation (CYP, P, N, CRN)
- Where there are questions over eligibility or a concern about the safety of a study ensure there is timely communication between the research and clinical teams (P, N, CRN)

Recommendation 2.2: Recognise the importance of the initial contact with CYP and parents

- Parents are supportive of being approached by research staff provided staff are clearly identified, professional, courteous, display a clear ID badge and show tact in their timing

Section 2: Recruitment

and sensitivity of approach (P, N, CRN)

- Liaise with clinical staff to ensure research staff are fully informed about personal circumstances, parental responsibility and show sensitivity in timing (N, CRN)
- Research staff require training to manage difficult conversations and develop confidence in the approach (CRN)
- Parents value the opportunity to make decisions jointly; with their child where possible and with their partners/ spouses if applicable. Strategies that promote involvement such as offering to meet with both parents and showing flexibility in availability are valued (P)

Recommendation 2.3: sensitive and timely communication during and after recruitment is vital to the informed consent process

- Be clear what the study outcomes are to enable parents to understand the relevance of the study to them (P, N, CRN)
- Identify (where appropriate) to CYP and parents how research has informed current care (CYP, P, CRN)
- Ensure there is a clear outline of what is uncertain or unknown without creating anxiety. Families can feel reassured by having what is 'normal' care and creating doubt about this is anxiety-provoking for them (P, CRN)
- Ensure there are designated times for questions about research conduct (P, CRN)

Recommendation 2.4: it is essential that CYP are involved as much as they would like throughout the whole research process

- There are challenges to CYP joining in discussions about research when they are unwell and in hospital due to fatigue, feeling unwell and medications, particularly if they are in a high dependency or critical care area such as PIC. The approach should (wherever possible) be at a time when the CYP is awake and able to join in discussions. Researchers should address them directly (SC, CYP, P, CRN)
- Liaise with clinical staff and parents to determine the optimum time and manner for approach and whether there are any communication needs or tools that are required (SC, CYP, P)
- Involvement should be assessed on an individual basis, rather than on age. There is a suggestion this could start from age 5 years. However best practice is to consider

Section 2: Recruitment

involvement with all CYP (SC, CYP, P, CRN)

Recommendation 2.5: researchers need to engage and collaborate with clinical staff

- Visible engagement with clinical staff is important to families. They want to see their clinical team have had input to determine if the study is appropriate for their child (CYP, P, N, CRN) (See *Recommendation 2.1*)
- This liaison needs to be evident throughout the PK research process from determination of eligibility, to timing of approach, to liaison over sample collection (P, N, CRN)
- Parents find it helpful to understand which staff are undertaking what roles so it is clear whom to approach with questions. This clarity of roles is particularly important for research conducted during emergency situations (P)

Recommendation 2.6: researchers need to consider influences on CYP and parents making decisions about participation in PK studies and address these where possible

- Helping others was regarded as extremely important to CYP and parents in PRESCRIBE. Communication about the study needs to emphasise the benefits for future service users, particularly where there is little or no benefit to the individual themselves (see *Recommendation 1.6*) (SC, CYP, P, N, CRN)
- There is a strong sense of group identity within some specialities so helping others might be a stronger motivation for some CYP and parents (P, CRN)
- If there are few treatment options available, some families can be highly motivated to participate. This requires sensitive handling, particularly if there are issues about being ineligible after review (CRN)
- Many PK studies are regarded as having 'no benefit' to the individual by researchers. However, researchers should avoid presumptions about what participants perceive as a benefit (P)
- Recruiting CYP on 'routine medications' is felt to be more challenging. This requires researchers to be realistic about recruitment targets (see *Recommendation 1.7*). This also requires researchers to review if there are any benefits that can be added for the individual patient (P, CRN)
- PK studies should allow the use of clinically indicated central venous lines (CVL) or arterial lines wherever possible to avoid the placement of additional cannulas (SC, CYP, P, N, CRN, R&D) (Errington et al., 2016)

Section 2: Recruitment

- Preparation and advanced notice of research should be considered in research conducted in emergency situations (see *Recommendation 1.2*) (CYP, P, N, CRN) as can deferred consent (see *Recommendation 1.4*) (SC, CYP, P, N, CRN) (CONNECT Advisory Group, 2015, Woolfall et al., 2015a)

Recommendation 2.7: extra 'research' appointments are not favourably viewed

- Extra appointments are challenging for CYP and parents and need to be avoided. Consider how to add research activity to clinically indicated appointments or liaise with clinical colleagues to add clinical assessments into research appointments (SC, CYP, P, CRN)
- Where appointments are required, researchers need to consider being flexible with appointments. Consider after school or weekend appointments or home visits to reduce the impact of missing school and parents having to take time off work. (SC, CYP, P, CRN)
- Where extra appointments are required, researchers need to consider resources required to make them interesting or fun, such as DVDs, computer games, stickers, certificates (P)
- If extra visits are required, the study should pay travel expenses or car parking to facilitate attendance (P, CRN)
- The study should also consider subsistence support and child care if required (P, CRN)
- Overnight stays should be avoided. If these are unavoidable, consider the use of a (funded) hotel to facilitate the family's attendance (CYP, P, CRN)

Recommendation 2.8: researchers must consider analgesia and non-pharmacological interventions

- Regardless of whether there is benefit to participants from participation researchers must consider reduction of pain and distress for CYP associated with blood sampling and make provision for the use of local anaesthetics, distraction and play therapy if required by service users (SC, CYP, P, CRN, R&D)
- Analgesia and play therapy need to be addressed in study protocols and adequately funded through research resources (P, CRN)

Section 3: Medication

Section 3: Medication
Recommendation 3.1: researchers need to consider the trial formulation carefully
• A pharmacist needs to be involved at the approval process to read and review the protocol for feasibility (CRN, R&D) • Participants need clear pictorial information so they are enabled to understand the actual size and shape of tablets or placebo medicines (P, CRN) • Palatability, colour and smell of medication can be significant problems for CYP. Formulation work is essential to ensure the drug can be administered and tolerated by the target participants (SR, CYP, P, N, CRN) (Kemper et al., 2011, Baguley et al., 2012) • Patient and public involvement (PPI) work would help with determining acceptability but this needs to be conducted early on to allow for changes to be made (R&D) • Researchers need to consider compatibility of medications with drinks or food and provide advice to families to allow them to make informed decisions. Without this, parents may administer the medication in ways which could affect the PK data (P, CRN) • PPI is required to ensure there is support for a change in formulation before a trial opens to recruitment (CYP, P, N, CRN) • Ensure there are no safety issues for patients before approaching them with a change in preparation, for example that there are no contraindications to taking a tablet such as a poor swallow (CYP, N) • Medication delivery must be in accordance with Hospital policy unless there is a protocol variation which is approved by pharmacy and R&D, for example the use of a blinded trial medication (N, CRN)
Recommendation 3.2: researchers should offer clear advice to CYP, parents and health care professionals about preparation and administration of medications
• There needs to be clear guidelines on the prescription of trial medication to ensure there is clarity in dosing and what to do when levels are required to reduce the potential for error (SR, N) • There needs to be clear, succinct guidance for parents and nurses on how to administer

Section 3: Medication

trial medication including (where appropriate): guidance on crushing of tablets, drug stability data, appropriate dilution (N, CRN) (Standing et al., 2005)

- Researchers need to educate clinical staff regarding documentation of the time of drug administration and the time of sample collection. It is vital to know the exact times medications were given (N, CRN) (Brundage et al., 2004)
- Study guidance needs to address the specifics about what to do in the event of a dosing error in a PK study as this will affect the reliability of the data (SR, N)
- The study protocol needs to address what to do in the event of vomiting or expulsion (rectal route) as this will have a significant impact on PK measurements (SR)
- The study protocol needs to provide guidance to staff on what to do in the event of being unable to administer medication at the designated time due to IV access unavailability, competing demands for access and a lack of appropriately trained staff. Guidance should include how this should be documented, whom they need to notify and what to do about subsequent PK measurements (N, CRN)

Recommendation 3.3: a PK study needs to have the appropriate resources to facilitate timely medication administration

- Ensure there are research staff available to support clinical staff in drug administration to ensure the correct dose is administered at the correct time (N, CRN) (Oliver et al., 2004, Dupuis et al., 2006)
- Ensure clinical staff have sufficient and appropriate resources to deliver the medication, particularly for intravenous (IV) delivery; for example, there are sufficient, appropriate IV pumps to avoid delays in trial medication administration (SR)
- Provide clear documentation /study aids which enable staff to accurately and clearly document times of administration Suggestions include slips attached to prescription charts. This is best developed on a study by study and site by site basis, informed by local practice (N, CRN)
- Provide clear documentation / posters that a patient is in a study to reduce the potential for prescription errors or changes outside of protocol guidelines (N, CRN)

Section 4: Sampling

Section 4: Sampling
Recommendation 4.1: wherever possible blood samples should be taken from clinically indicated intravascular catheters
• Use of an intravascular catheter (arterial line /CVL[3]) is supported by service users and health professionals (SC, CYP, P, N, CRN, R&D) (Salazar, 2003) • Where a study protocol does not allow sampling from a CVL and requires placement of a peripheral cannula this should be clearly identified within the PIS, including visual aids to assist with understanding procedures and devices (CYP, P, CRN) • CVL or arterial lines should be accessed in accordance with hospital policy by staff trained and competent to do so (N, CRN) • Wherever possible additional sampling should be minimised to reduce the risk of infection (P, N, CRN) • Where possible strategies of opportunistic sampling (where samples are taken alongside clinical indicated samples) should be utilised (N, CRN) (Thomson and Elliott, 2011)
Recommendation 4.2: PK study protocols should consider the placement and care of cannulas
• If additional cannulas are required for sampling, consider siting during anaesthesia (if applicable) to minimise pain from insertion or consider local anaesthetic cream to minimise discomfort from venepuncture (see *Recommendation 2.8*) (SC, CYP, P, CRN) (Abdel-Rahman et al., 2004, Vilo et al., 2008) • Consider the location of the cannulas, particularly if there is a requirement for two in contralateral limbs. Where possible, avoid incapacitating both hands (CYP, P, CRN) • Cannulas are the least preferred method for sampling for PK studies amongst CYP and parents. Consider the use of capillary samples instead if samples are of a minimal volume and only a few samples are required (CYP, P) • Action to be taken in the event of a cannula failing to 'bleed back' should be outlined,

[3] CVL is used to represent all forms of central lines, including those inserted for long term use such as a port-a-cath and those inserted for short terns used, such as those used on PIC.

Section 4: Sampling

particularly if there are restrictions on the sites where a cannula can be sited. This needs to clarify the issue of documentation of times of the sample and what to do if the sample is outside of a sampling window (N, CRN)

- The maximum number of attempts at resiting cannula should be discussed with CYP and families and documented clearly to help address anxiety amongst CYP (P, CRN)
- Continuity of personnel siting cannulas should be offered wherever possible, particularly if there are issues surrounding cannulation (CYP, P)

Recommendation 4.3: consider sampling volumes carefully

- A protocol should identify individual and total amounts to be taken, i.e. the amount per sample plus a total volume to be sampled (N, CRN)
- The PIS should provide clear information to indicate how much total volume is taken and how long it would take the individual to replace or regenerate this blood volume (SC, CYP, P, N, CRN)
- Consider stratified guidelines; with different volumes for different age groups, particularly for neonates and infants (N, CRN)
- Refer to guidelines within the study protocol and PIS to indicate the safety of sampling (CYP, P, N, CRN)
- Safety for the individual participant is paramount. Engage with clinician to determine if the sampling strategy poses any issues for the individual CYP (P, N, CRN, R&D) (see *Recommendation 2.1*)

Recommendation 4.4: consider the sampling regime and care of the sampling line

- If a cannula is to be used for sampling, consider preserving cannula patency through the use of saline or heparinised saline (CRN)
- Educate and train clinical staff about the sampling regime through targeted education and training (N, CRN)
- Support clinical staff with the sampling regime through allocated research staff to assist with or conduct sampling (at clinical staff discretion) (N, CRN, R&D)
- Educate staff about the importance of accurate documentation of sampling time (N, CRN, R&D)

Section 4: Sampling

- Research staff should provide clinical staff with the correct bottles, correct forms and labels for the required PK samples (N, CRN, R&D)
- If the research protocol allows the use of levels taken as part of routine therapeutic drug monitoring, ensure staff are educated to the importance of accuracy in the documentation (N)
- Minimise sampling requirements outside of office hours (8-5pm), particularly if the CYP is not an inpatient (N, CRN)
- Minimise requirement for overnight stay whenever possible by reducing sampling requirements at 12 hours (CYP, P, N, CRN)
- Identify a designated clock so the same clock is used for timings and this should be documented clearly on the accompanying paperwork (CRN)
- The time point '0 hours' will be defined as the pre-dose time. All the consecutive time points need to be calculated from the point of medication administration (CRN)
- Samples will be taken at the defined time points following on from this. Paperwork should identify what these are, the sampling window available (if any) and allow space for documentation of what time the samples were actually taken (CRN)

Recommendation 4.5: consider alternative strategies for the conduct of PK studies

- Opportunistic sampling reduces unnecessary access to lines and potentially reduces infection risk (see *Recommendation 4.6*). Researchers need to ensure monitoring of total blood sampling occurs to ensure safety of the individual patient (SC, CYP, P, N, CRN)
- Researchers should consider the use of non-blood samples, such as urine or saliva which are perceived to be 'less invasive' by CYP and parents (SC, CYP, P, N, CRN) (Royal College Paedatrics and Child Health, 2004)
- This approach could be considered if catheterised (for clinical indications). If CYP are not catheterised or CYP cannot void on demand need to consider how samples would be collected (N, CRN)
- There needs to be clear instructions within a study protocol on how to obtain saliva specimens and what to do for insufficient samples (CRN)
- If sampling is to include scavenged samples (leftover clinical blood samples) education is

Section 4: Sampling

required to ensure there is accuracy in documentation (see *Recommendation 4.4*) (C, CYP, P, N, CRN, R&D) (Wade et al., 2008, Thomson and Elliott, 2011)

- Randomised sampling windows where patients have the same number of samples taken but are randomised to different sampling frames are felt to be confusing for staff and parents (P, N, CRN)
- Making results available for clinical care was popular amongst CYP, parents and research staff who participated in PRESCRIBE. This requires samples to be processed immediately so the results are available contemporaneously to inform clinical care givers (CYP, P, CRN)

Recommendation 4.6: Safety of participants must be paramount

- Reference to safety guidelines to indicate safe levels regarding volume of blood is supported by service users and health care providers (CYP, P, N, CRN) (see *Recommendation 4.3* and *Recommendation 4.5*)
- Stratified volumes, according to age or weight would be useful to demonstrate consideration of body size (see *Recommendation 4.3*) (N, CRN)
- Variation in sampling practice is a concern, particularly in relation to scavenged sampling strategies. Education and training of clinical staff are required to reduce variability in sampling volume and discourage staff from taking more blood than required (N, CRN)
- Researchers should engage with clinical colleagues to determine the appropriateness of a participant entering a study from a safety perspective on blood sampling and encourage review throughout the sampling period (P, N, CRN, R&D) (see *Recommendation 2.1*)

Section 5: Processing

Section 5: Processing

Recommendation 5: researchers need to consider the storage, transportation and processing of samples

Section 5: Processing

- Clinical staff need to be issued with clear guidance on the sampling bottles to be used, the volumes required and labels to be applied (see *Recommendation 4.4*) (SR, N, CRN, R&D)
- There needs to be clear guidance on how and where to store samples and specific instructions on transportation, including accompany documentation. Instructions need to cover what to do if there are problems with each of these steps and who to contact (SR, N, CRN, R&D)
- The study assay needs to be thoroughly developed (SR)
- Resources need to be allocated to the staffing required to process samples taken throughout the 24-hour period, including staff to transport samples to the labs at night-time (CRN, R&D)

Section 6: Outcomes

Section 6: Outcomes

Recommendation 6.1: Conduct of PK studies require a positive attitude with value placed on the outcomes from the study

- Positivity towards research needs to be evident from all personnel, not just research staff (P, N, CRN)
- There needs to be evidence of the value an organisation places on research, with an emphasis that research is integral to improving clinical care (see *Recommendation 1.1*)

Recommendation 6.2: results from PK studies should be fed back to participants

- Ensure patients and their families receive feedback about study results, what was done with the samples they provided, what the outcome of the study was, what was the impact for clinical care and any research which will follow on from this (P, CRN)
- Provide patients with staff contact details for questions or further information and how families can contact researchers if they would like to participate in any future research

Section 6: Outcomes

(P, CRN)

- Consider the use of social media to feedback about trial outcomes (see *Recommendation 1.5*) (P)

Recommendation 6.3: PK studies must be adequately resourced with staffing support and minimise additional work for clinical staff

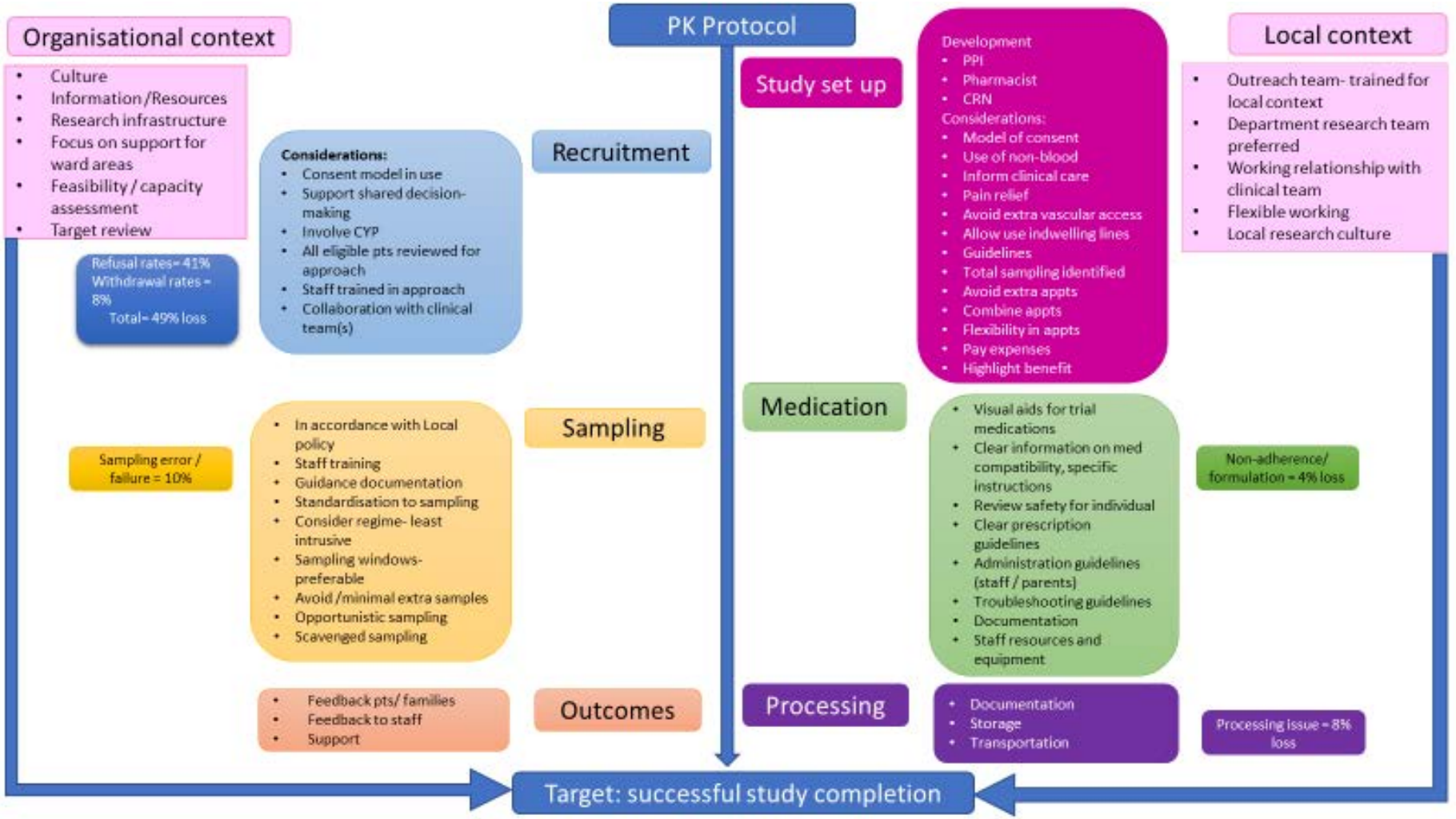
- Trial activity should be planned for office hours, wherever possible, and utilise designated research facilities where available (CYP, P, CRN)
- Overnight stays should be avoided wherever possible (see *Recommendation 2.7*) (CYP, P, CRN)
- Ensure senior staff in clinical areas are aware of sampling requirements so they can support their junior staff (N)
- Research support should ideally cover at least 60% of research activity and should be flexible to accommodate busy periods and cover 7 days /week (N, CRN)
- Support should be negotiated with the clinical nurses/ team to determine what help is required (N, CRN)
- Extra workload for clinical staff should be minimised, even in areas where there are 1:1 staffing ratios (SC, CYP, P, N, CRN, R&D)
- Research support should ideally come from a department specific research team, fully trained and familiar with the specific context of research (N, CRN, R&D)
- If a model of outreach support is utilised, staff need to be trained and assessed to have the skill sets required to support clinical staff (N, CRN, R&D)
- Training of clinical staff by research staff is essential to ensure smooth running of the study (*Recommendation 4.4* and *Recommendation 4.6)*. This needs to cover key aspects of the study and signpost staff to where further information can be sought (see *Recommendation 6.1*) (N, CRN)

Section 7: Context of research
Recommendation 7: consider the location of the PK study at the outset and throughout the study
• As an outpatient, CYP and parents are most supportive of research taking place in designated research facilities (CYP, P, CRN) • For inpatient studies avoid conduct within ward environments unless the study is adequately supported by research staff (P, N, CRN, R&D) • PIC is felt to be an appropriate place to conduct PK research, although research support must still be considered (see *Recommendation 6.3*) (CYP, P, N, CRN, R&D)

10.5 Impact on PK design

The scoping review established that the median number of participants in a PK study was 23. If this study was aiming to recruit and collect samples from 23 participants within 6 months, (taking into account that 70% of potentially eligible participants and their data could be lost or excluded from analysis) this study would need up to 26.8 months to obtain complete data. If these rates could be halved through tackling reasons for refusal / withdrawal, medication issues and sampling failures then this could have a significant impact on the ability of a study to recruit to time and target. Implementing the recommendations into a study design is obviously highly dependent on the individual medication under investigation; however, an implementation guide has been developed *(*see *Figure 69).*

Figure 69: implementation of PK recommendations into a pilot PK study design



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1. Appendix 1: Vignette and preparation material (CYP)

Vignette and preparation material utilised with sessions with CYP. This material was adjusted for each stakeholder group but the 'typical' PK study situation core components remained consistent

Birmingham Children's Hospital NHS
NHS Foundation Trust

What is Pharmacokinetics?

•When you are sick you sometimes have to take medicine. The amount of medicine we give can be difficult to get right because all children are different and growing at different rates.

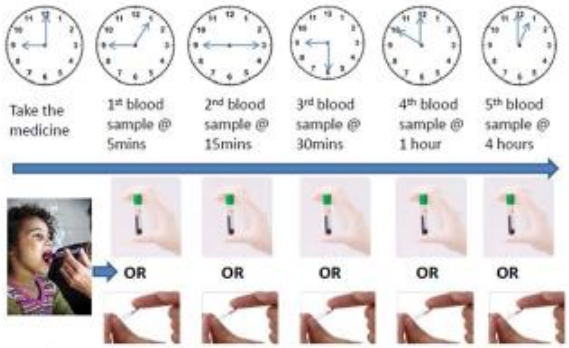
•Doctors and pharmacists have to work out
- How much medicine do we give (the dose)?
- How often do we give the medicine?
- How long do we give it for?

•For a medicine to be successful, the staff must find the correct balance of good and bad effects. Sometimes either the dose of the medicine (how much) or the schedule on which it is given (how often or how long) will need to be changed to gets this balance right.

Birmingham Children's Hospital NHS
NHS Foundation Trust

What happens in a PK study?

You take your medicine at the beginning, and then samples (most often blood) are taken (either from a small plastic tube in a vein you already have called 'a cannula' or from a finger prick) at regular times.
The number of samples taken will vary



The laboratories then checks that the level stays in the range that is good for you. This can help the Doctor to know how to prescribe your medicine

Birmingham Children's Hospital NHS
NHS Foundation Trust

A 'typical' PK study

•**Who's included in the study? All** children receiving a medicine as a hospital inpatient can be included (babies – 16years).
•**What is different?** The medicine would be the same whether you were in the study or not but if you said 'No' you wouldn't have any blood samples taken.
•**What sample?** Blood can be taken from a plastic tube in the arm ('a cannula')
•**Where?** The study might say you have to have it put in your hand or a specific arm (you can't choose where they put the cannula).
•**How often do they take blood?**

1. Just before the first dose of the medicine
2. 15 minutes after the medicine
3. 1 hour after the medicine
4. 4 hours after the medicine
5. 8 hours after the medicine
6. 12 hours after the medicine
7. 16 hours after the medicine
8. 24 hours post drug

They have to take the level within 5 minutes of each time.

Birmingham Children's Hospital NHS
NHS Foundation Trust

Problems?

- Taking medicines
- Taking blood samples
- Samples going to the labs
- Coming to hospital

Birmingham Children's Hospital NHS
NHS Foundation Trust

Solutions?

- **Population PK:** more patients in the study, less samples from each patient

e.g.

10 patients: give 6 samples each

30 patients: give 3 samples each

- **Sampling windows:**

	Bloods	Bloods	Bloods	Bloods
Group 1	5 mins	30mins	2 hours	8 hours
Group 2	10mins	1 hour	4 hours	12hours
Group 3	20mins	1.5hours	6 hours	18 hours

- Using central lines or ports
- 'Left over' blood from other samples
- Other body fluids: wee, spit
- Home visits instead of hospital visits

2. Appendix 2: Interview schedule: CYP

FOCUS GROUP INTERVIEW SCHEDULE – Group 1b: children and young people (approved by REC)

Aim:
To explore the knowledge and attitudes that exists towards pharmacokinetic research amongst children and young people

- To determine what knowledge children and young people have about pharmacokinetic research
- To explore attitudes children and young people have towards PK research
- To explore the barriers children and young people perceive towards participation in PK research
- To explore the factors that facilitate PK research taking place

Method: The aim is to pose the questions below in a focus group forum although there is the option of conducting the interview on a one to one basis, depending on individual preference. The structure of the session is to some degree dependent on the interaction between participants therefore the schedule will be flexible according to the conversations generated. The session facilitator will guide the session to ensure the areas below are covered as well as allowing new areas of enquiry to emerge.

Ground rules will be outlined and then there will be some ice breaker games to allow the group to know a little about each other before the interview schedule formally begins.

Opening: "You have been asked to take part today because you have visited Birmingham Children's Hospital either via the Emergency Department, the Wellcome Clinical Research Facility or one of the wards and therefore you know a little bit about what happens when you come to hospital".

Question	Rationale for asking the question	Prompts
1. Could you tell me how about your experiences of coming to Birmingham Children's Hospital?	This will start the flow of the interview and allow the participants an opportunity to express their level of experience. This will help ensure I know who the respondents are so we can show sensitivity to their individual circumstances. The prompt questions will lead on from the main questions on the left and allow us to explore the experiences each participant has had and draw out the similarities between experiences. Although this will involve naming teams and Consultants this information will be anonymised in transcription. It is of use to understand the experiences the individuals have had and to help them to open up about their own	Do you know the name of the Consultant or team who usually manage your care? Do you know how long you've been seeing them? How often do you have to come to the hospital? Which departments do you usually visit? Have you had to stay in overnight or longer on one of the wards?

	experiences.	
2. Can you describe the best bits about coming to hospital?	This is a difficult concept to explore but I'm looking to determine if the participants have had positive experiences & demonstrate confidence in their care providers. There is evidence in the literature that such relationships can influence recruitment to research and this is a theme I'd like to explore.	What do you like about the team of people you see? Are there any people you especially like to see when you come to hospital? What is it about * that makes you feel positive about coming to hospital?
3. Can you describe the worst bits about coming to hospital?	I want to explore their perspective of the worst bits about a hospital visit because these will impact on their decision making about research. The systematic review indicated that the biggest areas for refusal of research and withdrawal were additional blood sampling requirements and additional hospital visits. We need to discuss this further with children and young people directly so we can clarify how much of a problem these are and then allow them to explore solutions/ ways of minimising these.	How do these experiences make you feel? How do you / how did you cope with these experiences? How important is it to you that these episodes are kept to a minimum?
4. What do you understand about the term 'Research'? Do you think this is important in health care?	As the group have had little introduction to the topic of PK research we'll start by asking them about their understanding of 'research' and whether they feel this is important in health care. From this we can then lead on to talking about the more specific area of PK research. Without setting the context I think we would be endanger of losing their understanding and concentration.	Have you ever taken part in a research study in health care? Have you ever heard of a type of research called 'pharmacokinetic research'? Are you on any medicines that have ever had to have a level taken, for example medicines to help reduce or control 'fits'?

Using power point a simple vignette will be used. If the schedule is being used in the context of a one to one interview then this will be printed out as a handout.
Key points highlighted will be:

- Usually of a medicine the child is already receiving.
- Usually involves blood samples
- Involves knowing exactly when a medicine is given
- Involves knowing exactly when blood samples were taken
- Often a protocol states in advance the times blood samples need to be taken (not flexible)
- May involve sampling up to 24 hours but some studies have asked for samples at outpatient appointments for weeks and months afterwards.

4. What do you think about taking part in a study like this? Depending on the response we will then discuss issues in a step by step method: <u>Medicines</u> * How do you feel about taking your medicines at exact times? <u>Blood samples</u> * How do you feel about having blood taken to measure medicine levels?	I want to know their initial reactions to a more 'classic' PK study design with a structured approach to the taking of the medicine and the sampling requirements. I want to know what their concerns would be and if there are any factors that make them say 'No' immediately. It is important to address the individual areas. For example the issue of taking medicine at particular times might not at first seem a big issue but it might be if it meant it had to be dispensed by a health professional and taken at 8am on an empty stomach, so a number of variables can be controlled. Some studies might involve comparing two methods of delivery so children might be asked to take the medicine in a different formulation. A small number of participants in the systematic review had to withdraw because they could not take the supplied formulation. Blood sampling is identified as the biggest issue affecting recruitment & withdrawal from PK studies but also the physical difficulties of obtaining sufficient blood and the right number of samples caused the loss of a large number of participants. This area has not been explored directly with children & young people previously and it is vital that we explore these issues.	How does the study design make you feel? Is there anything about this that makes you worry? Prompts to explore these areas further: <u>Medicines</u> If you've taken medicine have you always taken it at the exact time? What difficulties do you think there might be with this? Would it make a difference to you if you had to be admitted to hospital so they could give you the medicine at the exact times? How would you feel if you were asked to take part n a study which gave you the same medicine you're usually on but in a different form such as a tablet? What if it involved you taking medicine at school in order to match the times? Would this matter to you? Have you ever had any problems with taking a medicine such as the tablets being too big or not liking the taste? Have you ever been sick just after taking a medicine? If you have what did you do? Have you and your parents ever worried about whether you might need to alter your medicine dose? <u>Blood samples</u> If we could take blood samples from a cannula or from a central line (if you have one) would this affect your decision to take part? What if this was not possible, is there a limit on how many times you would agree to have blood taken? Would it matter to you if they didn't tell you how much blood they were taking? Does it matter to you what times the blood samples are taken? Would you be happy to have blood taken even if it involved

Additional visits * How do you feel about having to come to hospital for extra appointments?		being woken up in the night? Additional visits Would missing school be a concern for you or your parents? Do you think your parents would have worries about getting you to the appointments such as having to take time off work?
Using power point there will be pictorial guides to some of the ideas the literature suggests could facilitate PK studies. Where the schedule is used in a one to one interview the slides will be printed out as a handout. • Population PK modelling • Randomised sampling windows • Sampling from a central line • Sampling from an arterial line • Dried blood spots		
5. We have some suggestions for ways to improve some of these factors. What are your thoughts on: Population PK * less samples per patient but we involve more patients and group all their data together? (population PK modelling) Sampling windows * another option is that different sets of patients have blood taken at different time periods eg group 1 have blood taken at 10 mins, group2 have blood taken at 20 mins. Does that seem like a good idea to you? Using central lines / arterial lines * using 'central lines' in a big vein wherever possible? * Patients in intensive care often have a line in an artery so we can take bloods easily and quickly, do you think this would be a good time to measure medicine levels?	Following on from the systematic review we have identified a number of facilitating factors which we are keen to explore. The questions to the left reflect emerging themes from the literature which require lay discussion. Population PK modelling has become more common because it makes the most of sparse samples, particularly in vulnerable patient groups and sampling times can be flexible. Randomised sampling windows have been described in the literature alongside Population PK modelling but there has been no work to determine the acceptability of these with children and young people. In the literature there has been reluctance to use existing central lines, particularly if the drug is being administered via the line. However there is some evidence to suggest that there is no difference in levels provided the naive lumen is used and this would seem to avoid the need for additional venepuncture.	Population PK Would it seem better to you if you only had to give 2or 3 samples and we could be flexible about what times we took them? Sampling windows Would a time 'window' eg 10-15 minutes be preferable to an **exact** time? Using central lines / arterial lines If you had a 'central line' in a big vein and we didn't use it to take bloods how would that make you feel? People in intensive care are usually very poorly or recovering from being very poorly. Does this affect what you think? How important is it to you that we take as little blood as

<u>Dried blood spots</u> * How would you feel about us using dried blood spots? Although this might mean a finger or toe prick it would then only need a tiny volume of blood. <u>Left over blood</u> * At the moment any blood taken for 'routine purposes' is put in a bin after use. If there was any blood 'left over' would you be happy for us to use this to measure medicine levels? <u>Other body fluids</u> * Would you be happy to take part if we measured the medicine levels in a different body fluid, not blood such as spit or urine (wee)?		possible? Would you prefer it if we took blood only at the same time as bloods taken for 'routine purposes'? <u>Dried blood spots</u> Which is more important to you: the number of 'stabs' that take place or the amount of blood taken each time? <u>Left over blood</u> How would you feel about having leftover blood used if you hadn't said yes to this being used? <u>Other body fluids</u> Would you feel happier if it was measured through urine (wee) or saliva (spit)? Would you be happy if we used any fluids that would otherwise go into a bin such as chest drain fluid?
6. How important is it to you that there is a person you can contact with any questions about the study?	Anecdotally staff report that a research study can fail if it is not appropriately staffed and resourced but this factor has not been explored within the context of PK research and not from the perspective of participants.	Studies like this are 'extra' to normal care. Would it worry you that the hospital staff might have extra work to do because of the study? Do you think that we should provide extra staff to do all the jobs involved such as taking the blood and sending it to the labs? Would it put you off taking part if there was not a names person / team of people to support you?
7. Do you think it's important for us to include **all** ages of children and young people in this type of research?	In the papers included in the systematic review there was large variation in the age of the participants included in the study. Neonates were only specifically included in 8% of the papers and infants < 1 year in 52%. In other types of research there has often been a reluctance to invite groups such as those with a life limiting condition or those who are on intensive care. We think this is a vital area to explore with	Do you think there are any groups we **shouldn't ask?** What do you think about asking parents of premature babies? Parents of children who are very poorly and might die? What about if Mums and Dads are very upset. Do you think we should ask them?

	children and young people with direct experience of health care.	What do you think we should do if parents do not speak or read English? Mums and dads who the Doctor thinks will say 'No' What should we do about mums and dads who can't visit the hospital very often because they live far away or because they have to stay at home and look after their other children? If we think Children are not taking their medicines properly do you think we should still ask them to take part?
8. After everything you've heard about PK research would you say 'yes' if we asked you to take part in a PK study?	I've left this as a closed question because I think it's important to draw them into an answer before exploring why their immediate response is what it is. It will be interesting to compare this to the responses we get on the questionnaire when they might not have fully understood what was involved.	What would make you say 'Yes' / 'No'? What makes you worry about taking part? What is the biggest factor for you in deciding yes or no? Would there be anything that would make you change your mind? Do you think your view has changed since you've been taking part in this project and you've learnt more about it? Do you think you would have different worries to your mum or dad? Do you think research like this is important? How do you feel about the fact that there isn't much research like this taking place at the moment? Do you think it's ok for us to approach children and their parents to take part in PK studies?

Thank you for taking part.

3. Appendix 3: Full list of Participant Information Sheets for all stakeholder groups, consent and assent forms

For the purposes of space not all versions are included within this thesis. Forms highlighted in yellow are included below.

1. **Participant Information Sheet Schools**; version 1.1, 07.03.14
2. **Participant Information Sheet 8-10yrs**; version 2.0, 17.12.11
3. **Assent form child 8-10 yrs**; version 2.0, 16.12.11
4. **Participant Information Sheet 11-16yrs**; version 2.2, 10.04.14
5. **Assent form children and young people 11-16 yrs**; version 2.0, 16.12.11
6. **Participant Information Sheet for parents (child & young person's group)**; version 2.0, 16.12.11
7. **Consent form for parent (child & young person group)**; version 2.1, 23.01.12
8. **Participant Information Sheet**; Parent Focus group; version 2.0 ,16.12.11
9. **Consent Form for Parent Focus Group**; version 2.1, 23.01.12
10. **Participant Information Sheet for Nurses**; version 2.0, 16.12.11
11. **Consent form for nurses**; Version 2.1, 23.01.12
12. **Participant Information Sheet Clinical Research Staff- BCH**; version 2.0, 16.12.11
13. **Participant Information Sheet Clinical Research Staff - BWH**; version 2.0, 16.12.11
14. **Participant Information Sheet Clinical Research Staff –UHB**; version 2.0, 16.12.11
15. **Consent form Clinical Research Staff- BCH**; version 2.1, 23.01.12
16. **Consent form Clinical Research Staff - BWH**; version 2.1, 23.01.12
17. **Consent form Clinical Research Staff –UHB**; version 2.1, 23.01.12
18. **Participant Information Sheet Hospital Managers**; version 2.0, 16.12.11
19. **Consent form Clinical Research Staff**; version 2.1, 23.01.12

Appendix 3a: Participant information sheet for school children

Birmingham Children's Hospital

Steelhouse Lane

Birmingham

B4 6NH

07.03.2014

PRESCRIBE: Pharmacokinetic RESearch in CRitically Ill children: facilitating the BEst design

Dear parent,

We are writing to you to ask if you'd be happy for your child to take part in a **discussion group** and complete a short **questionnaire**.

This study is trying to determine the best way to carry out clinical trials in children by talking to children and young people and asking them what is important when we design a study. We would like to speak to children who have little or no experience of being in hospital to understand how they might feel if approached when admitted to hospital when ill.

Why are you asking my child?

Your child's school thinks it is important for children and young people to learn about medical research and has agreed to help the research team carrying out this study.

What do they have to do?

They will be asked to listen to a short talk about research into children's medicines and then feedback their thoughts through discussion groups which will be tape recorded and completing a short questionnaire.

The questions will ask about things such as:

- Taking medicines in different forms
- Having blood taken
- Coming to hospital for appointments

What are the benefits of taking part?

The PRESCRIBE team want to ensure that children and young people's views have been considered when designing research studies. The information we get from this work will help us to improve the design of studies for children in the future.

Will the information my child gives be kept private?

The questionnaire will not request any identifying information from your child such as their name so their responses will be anonymous. If any names are used during the discussion groups they will be removed when they are transcribed.

Who is involved in this research study?

The session will be carried out by Julie Menzies, a research nurse undertaking a PhD with supervision by Professor Marriott at University of Birmingham & Dr's Morris and Duncan at Birmingham Children's Hospital. The study has been reviewed and approved by National Research Ethics Committee South Central- Oxford A (12/SC/0051) and the Research & Development Department at Birmingham Children's Hospital.

Who can I get more information from?

If you would like to anything more about this work please contact [redacted] or [redacted]. If you would like any independent advice about how this study is being conducted please contact the Research and Development team at Birmingham Children's Hospital on [redacted].

I'm happy for my child to take part with this work during their visit, what do I need to do?

No action needed. Unless the school tells us you don't want your child to take part then we will include all children in the discussion session and ask them to complete a questionnaire.

I'm not happy for my child to take part, what do I need to do next?

Please let your child's teacher know and an alternative activity will be arranged on the day during the visit. They would then attend the presentations but would miss the group discussion work and completion of the questionnaire.

Appendix 3b: Participant information sheet and assent form CYP aged 8-10years

PRESCRIBE: Pharmacokinetic RESearch in the CRitically Ill: facilitating the BEst design

Dear

We are asking if you'd like to take part in a **discussion group** (called a 'focus group').

When children are sick they sometime have to have medicines. The amount of medicine we give can be difficult to get right because all children are different and they are all growing at different rates. We think it's important that more of this type of work takes place so we want to ask children and young people what is OK and what is **not** OK when we do this kind of work.

Why are you asking me?

You've been asked because you have been to Birmingham Children's Hospital and know a little bit about what happens when you come to the Emergency Department, outpatients department or if you get admitted to one of the wards.

What do I have to do?

We'd like you to come and meet up with a group of other children aged 8-16 years old to talk about your thoughts.

The questions will ask about your thoughts on things such as:

- Having blood taken
- Coming to hospital for appointments
- Ways of measuring the levels of medicine.

The session will last between 45 minutes and an hour and a half depending on how much everyone talks!

You will sign a form called an 'assent form' which says that you're happy to take part and your parents will sign a form called a 'consent form' which says they're happy for you to take part.

We'll give your parents money to pay for getting to the hospital or for parking the car and we'll have some drinks and biscuits for you all.

Your mum or dad are welcome to wait for you but the session is for children and young people only as we want to hear **your** views.

We'll run some other sessions for parents at a different time to talk to us as we want to know their thoughts too.

Where will it be held?

The group will be held at the Wellcome Clinical Research Facility, which is on the ground floor of the main hospital corridor at Birmingham Children's Hospital.

Do I have to say yes?

No, not at all! It's up to you! It won't affect any of your normal care.

Is there any other way I can join in?

We know that some people don't like talking in front of other people. If you would prefer to talk to our researcher on your own instead we would be happy to do this. We can even come to your house if you would prefer.

Will joining in this study help me?

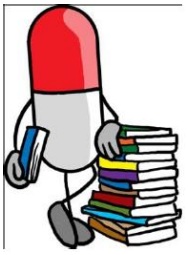
We cannot say that the study will help you. We hope that the information we get will help other boys and girls in the future because we will improve how we do this type of study and get more information to help Doctors prescribe medicine.

Will what I write be kept private?

It will. We won't write anything in your notes or tell your Doctor. The sessions will be tape recorded and then written out in full. If any names are used during the focus group they won't be written out. Also any other information such as ward names or places will be removed.

Any information will be stored on a secure password protected computer and no one will have access to this apart from the team who are running this project.

What will happen with the results of this work?



When we have finished the study the results (what we find out) will be written up in special scientific magazines. No one will know that they are your results because your name will not be in them.

We can send you a summary of the results if you or your parents would like to read them.

This information will help us make a guide for future researchers about the best way to do this type of study.

Contact details

The name of the person running this study is Julie Menzies.

If you or your mum or dad want to ask anything else about the study please contact 

[redacted]  or by phone on [redacted]

I'm happy to take part, what do I need to do next?

Your mum or Dad need to complete the form we've given to them so we know how best to contact you all to arrange the meeting.

Appendix 3c: Assent form for CYP 8-10years

PRESCRIBE: Pharmacokinetic RESearch in the CRitically Ill: facilitating the BEst design

Assent form for children 8-10 years (focus group)

V2.0, 16.12.11

Child (or if unable, parent on their behalf) to circle all they agree with:

Has somebody explained the study to you?	**Yes / No**
Do you understand what the study is about?	**Yes /No**
Have you asked all the questions you want?	**Yes / No**
Have you had your questions answered in a way you understand?	**Yes /No**
Do you understand it's OK to stop taking part at any time?	**Yes / No**
Are you happy to take part?	**Yes /No**

If any answers are **'No'** and you **don't** want to take part don't sign your name!

If you do want to take part, please write your name and today's date

Your name:_____Date:_____

Your parent or guardian must write their name here too if they are happy for you to do the study.

_____ _____ _____

Print name Signature Date

The researcher who explained the study to you needs to sign too:

_____ _____ _____

Print name Signature Date

Assent form child 8-10
Version 2.0 16.12.11

Appendix 3d: Participant Information Sheet for Parents (for their child to participate)

PRESCRIBE: Pharmacokinetic RESearch in the CRitically Ill: facilitating the BEst design

Dear Parent

Part 1: Invitation to participate

We are inviting you to ask if **your child** could take part in a discussion group ('focus group').

Why is this study needed?

We are trying to determine the best way to carry out a type of research called 'pharmacokinetics' in children. Pharmacokinetic data helps Doctors to decide what dose of medicine to give children, how often to give it and how to alter the dose as children grow and develop. This information is important to make sure that drug prescriptions are safe and the dose prescribed is not too high or too low.

Why are you asking me?

We're asking you because you and your child recently attended or your child was an inpatient at Birmingham Children's Hospital. We want to talk to children to ask them what is important when we design a study like this.

Part 2: what will happen if I say yes?

Do I have to say yes?

Taking part is completely voluntary. If you think this is something your child would be interested in doing then we'd like to invite them to take part in a focus group. We'll provide them with an information sheet which has been written for their age group. If you both agree then we would ask you to provide us with your contact details and we'll contact you to arrange a date. You will be asked to sign a consent form on the day of the focus group and your child will sign the form too. You will be given a copy of the information sheet and signed consent form to keep.

What happens during the study?

You will be asked to bring your child to attend the focus group. This focus group will be composed of 6-10 children who all have attended hospital at some point. The session will last between 45- 90 minutes, depending on how much they talk!

Refreshments will be provided and your travel costs will be reimbursed. The session will be for children and young people **only** but if you are interested in contributing to the topic we are running separate groups for parents which you would be welcome to join.

If your child would like to take part but doesn't like the idea of talking in a group setting *or* it would be difficult for you to bring them to hospital we can arrange for the researcher to come to your home and conduct a one to one interview there using the same questions.

What kind of things will they be talking about?

We want to know your child's thoughts and experiences on having blood taken, how they might feel about research which measures levels of medicine and whether there is anything that would make them feel more positive about this type of research. There aren't any right or wrong answers and all we're asking them to do is to join in the discussion.

Where will it be held?

The session will be held in the Wellcome Clinical Research Facility, which is on the ground floor of the main hospital corridor at Birmingham Children's Hospital.

What are the benefits of taking part?

Taking part will not help your child directly but we expect that the information we get from this study will help us to improve the design of studies for children in the future.

What are the possible disadvantages of taking part?

There is minimal risk from taking part. If the discussions do bring up any distressing memories for your child of being in hospital or attending hospital we will put you in contact with BCH staff for further support, particularly if there is a team who you already know. If the situation involves a complaint related to previous care we will refer you to the Patient Advice and Liaison Service (PALS). There is also a patient and family counselling service at BCH we can refer you to.

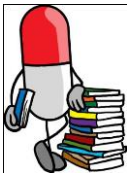
Who will know I took part? And is it confidential?

The session will be private and only the other people who took part will know. We won't write anything in your child's medical records notes.

The focus groups will be tape recorded and then written out in full by the researcher. If any names are used during the interviews then the researcher will remove them. Also any other information such as ward names or places will be removed. The audio-tapes and transcripts will be kept in a locked filing cabinet in a locked office. Only the researcher will have access to the audio-recorded data. The data will be collected and stored according to the Data Protection Act 1998.

If you wish to withdraw your consent following the focus group this can be done up to a week after the session, before the researcher transcribes the session. Please contact Julie Menzies on the contact details below if you decide you wish to withdraw.

What will happen to the results of the study?



We aim to publish the results of this research in a reputable medical journal and to share results at conferences. Confidentiality will be ensured at all times and your child will not be identified in any publication.

Who is involved in this research study?

The University of Birmingham is sponsoring this study. The Chief Investigator for this study is Julie Menzies. The study is funded through a scholarship from the West Midlands Strategic Health Authority through a Nursing, Midwifery and Allied Health Research Fellowship. All research in the NHS is looked at by an independent group of people called a Research Ethics Committee to ensure the interests of patients and their families is protected. This study has been reviewed by National Research Ethics Committee South Central- Oxford A and approved.

Who can I contact if I have any concerns about this study?

The name of the person running this study is Julie Menzies.

If you want to ask anything else about the study please contact

or by phone on

If you have any concerns about this research project or want any independent advice about how this study is being conducted please contact the Patient Advice and Liaison Service at BCH on or the Research and Development team at BCH on

I'm happy for my child to take part, what do we do next?

Please complete the form below which details your name, your child's name, contact details and preferred way of being contacted. We will then get in contact with you to arrange when the focus group will take place. If you are unable to attend a focus group or your child would prefer a one to one interview then we can make arrangements to conduct this at your home instead

Your name:

Your child's name:

How would you like to be contacted? Please tick your preferred method below and then add your details alongside.

☐ Post: my address is:

☐ Email: my preferred email address is:

☐ Telephone: my phone number is:

My preferred day for the focus group would be:

☐ A weekday, preferably:

☐ Weekends

☐ During school holidays

☐ **Not** during school holidays

Other:

My preferred time of day for the session would be:

☐ Mornings

☐ Afternoons

☐ Evenings

Your signature:

Please return in the stamped addressed envelope. If you misplace this please post to:

Julie Menzies

PICU Research Office, PICU, Birmingham Children's Hospital,

Steelhouse Lane, Birmingham. B4 6NH.

Thank you

Appendix 3e: Consent form for parents (CYP to participate)

PRESCRIBE: Pharmacokinetic RESearch in the CRitically Ill: facilitating the BEst design

Consent form for Parents (child and young person focus group)

V2.1, 23.01.12

	Please initial box
I confirm that I have read and understand the **Participant Information Sheet** dated **16.12.11** and version **2.0** for the above study. I have had the opportunity to ask questions and have these answered satisfactorily	
I understand that participation is voluntary and that I am free to withdraw my consent from the study at any time without giving a reason although I understand that this is only possible for 7 days following the focus group	
I give consent for the researcher to audio-tape the focus groups	
I consent to the use of anonymous quotes	
I understand that relevant sections of my child's medical notes may be looked at by responsible individuals from the research team, sponsor or from the NHS trust. I give permission for these individuals to have access to my child's records.	
I understand that my personal data will be processed for the purposes above in accordance with the Data Protection Act 1998.	
Based upon the above I agree to my child taking part	

_____

Name of Child

_____ _____ _____

Name of participant Signature Date

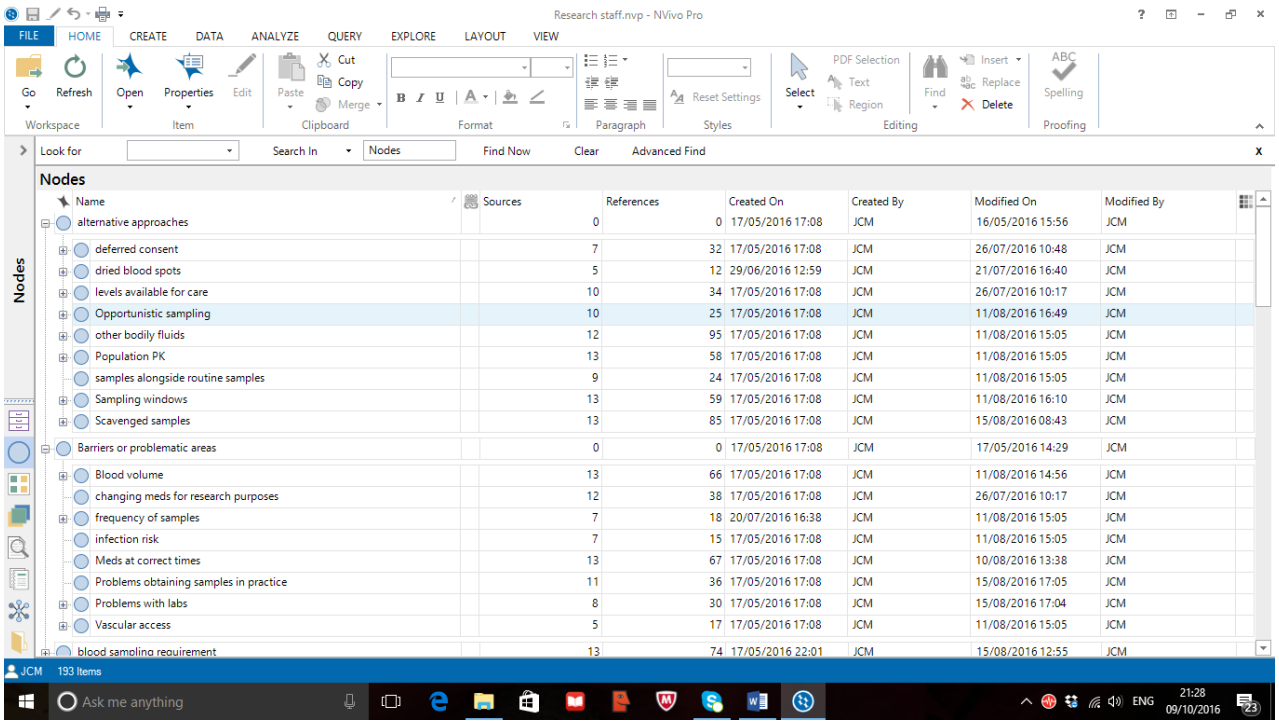
_____ _____ _____

Researcher Signature Date

4. Appendix 4: Summary of the coding process

Figure 70 demonstrates the coding system in NVivo 11. The nodes are listed and sources and respondents are listed. The pictures and screenshots are taken from interviews with research staff however the process was the same for all participant groups.

Figure 70: screenshot of the coding system in NVivo 11



The next step was to review the codes and try to classify them where possible, or re-code them, remove codes which were not fruitful or were subsumed in other codes. All nodes were then exported into excel for review (see *Table 67*).

Table 67: management & organisation of nodes. Deleted nodes in 'grey'

Name	Sources	References
access to novel treatments	8	27
alternative approaches	0	0
deferred consent	7	32
dried blood spots	5	12
levels available for care	10	34
Opportunistic sampling	11	28
other bodily fluids	12	95
Population PK	13	59
samples alongside routine samples	9	24
Sampling windows	13	72
Scavenged samples	13	86
Barriers or problematic areas	0	0
Blood volume	13	68
changing meds for research purposes	12	38
frequency of samples	7	19
infection risk	7	15

Meds at correct times	13	63
Problems obtaining samples in practice	11	36
Problems with labs	8	28
Vascular access	5	17
A line	9	22
cannulas	11	59
Cannulas bleed back	12	50
capillary samples	5	17
central line	11	54
blood sampling requirement	13	70
children's attitudes towards research	10	28
Communication	8	23
compliance	8	21
deleted nodes	0	0
adherence	3	6
'Guinea pig'	1	3
child involvement	2	3
non-nurses	2	3
blood sampling requirements	1	1
clinician decision	5	5
Coordination of care	3	4
preparation	1	2
medical cover	1	4
'Only treatment available'	2	2
opt in, opt out	1	2
Control	1	1
retention to study	2	4
Time	0	0
resentment	2	6
trust	1	1
inconvenience	1	2
assistance for vascular access	1	3
Workload	2	2
waste	3	3
Blood transfusion	0	0
prescription issues	0	0
Probs with meds at right times ORAL	2	5
Documentation	7	33
engagement with clinical team	9	68
experience	0	0
example drugs	3	6
Experience of PK in a study	13	57
Experience of PK in clinical practice	10	30
similar to PK studies worked on previously	8	15
extra workload	11	46
facilitating	0	0
Guidelines	12	53
relationship with clinical team	8	53
support	9	50
'outreach support'	11	82
PIC research team	5	10
families' attitudes	13	106
fear and pain	8	21
gatekeepers	6	16

hospital policy	3	7
Infiltrating the clinical area	6	20
magic cream	3	4
Not novel drugs, just routine	8	22
parents comparing	4	12
past experiences	7	18
perceived benefit- parents	8	26
piggy backed to clinical care	6	12
precision	11	72
preparation and organisation	13	59
priorities	10	32
protocol acceptability	7	47
recruitment	13	69
'research care'	8	18
Research context	0	0
location of study	13	108
Regime	11	51
Times of day	10	25
vignette	9	23
research facilities	10	36
research features	0	0
same clock	3	3
delegation log	4	4
tablet size	9	12
missing school	6	12
palatability	7	14
Extra hospital visits	8	26
avoid hospital	4	15
responsibility	12	34
staff knowledge and attitudes towards PK	1	1
all ages included	13	33
care for Pt in PK study	13	20
feedback from research	3	10
Further investigation	10	30
groups to exclude	10	29
Neonates	7	15
inclusive	4	13
Palliative	13	54
PK definition	13	30
research is important	9	18
Research vs clinical ratio	13	67
The approach	11	38
staffing issues	11	70
Training	11	39
unsocial hours staffing	8	20
valuing family's choices	4	17
'with my parent hat on'	3	16
withdrawal from study	10	17

The next stage was to condense these further into themes and this was achieved through mind maps. Each node was mapped to the core themes and also to context and facilitation the underpinning factors in I-PARIHS. Some nodes fitted into more than one category, so there was

some fluidity about their placement. Using the list of themes and sub-themes as a template, a framework matrix for each participant was created (see example in *Table 68* below).

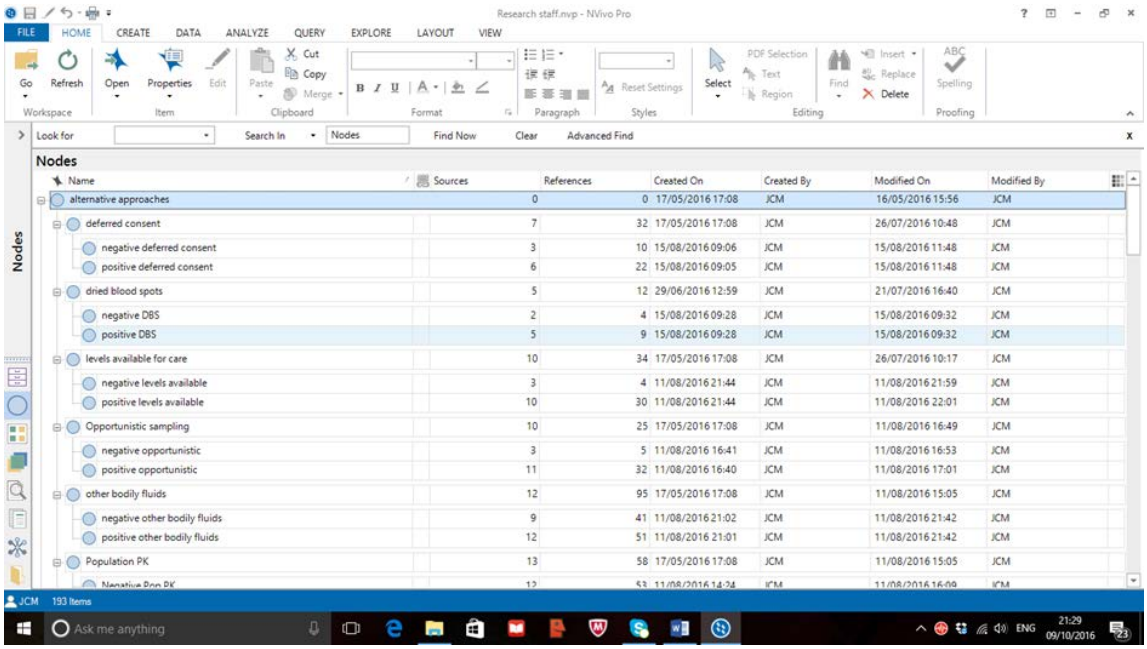
Table 68: participant 48 Framework

Participant 48	
Definition of PK	√
Experience of PK in a study	√ In WTCRF Challenges extra visits and sampling. Pain from cannulas
Experience of PK clinically	Not asked (has experience in a study)
Similar to PK study in the vignette	√
Problems with meds at right times	√ Oral better than IV as then only need 1 cannula
Access to new treatments / phase 1 Important to families	√ Volunteering for projects when no other options available. Good quote about desperation of people calling from all over the world about a study. Might be harder for studies where not novel treatment
Families attitudes	Motivated improve care for their child. Some altruistic but not as many
Children's attitudes	Distress / pain. Removal of choice (i.e. preferred places have lines)
Avoid / minimise hospital	Avoid overnight where possible- use of hotels option
Piggy backing to clinical care wherever possible	√ particularly bloods
Preparation and organisation	√ Key
Research facilities	Access to facilities important- WTCRF big help with this (if adopted)
Priorities- 'I'm a nurse first and then I'm a researcher'	Put parent and child first
Changing meds for research purposes	√ Problem for parents and children
Problem with protocols (protocol acceptability)	√ does it work locally? Review for individual pt. Doesn't fit with actual practice
Guidelines	MCRN guidance PI decision Clinical experience in recognising acceptability
Guidance	Very little in protocol on care of cannula Flushes
Problem with sampling requirements	√
Vascular access	Cannulas- pain, lack choice on location Capillary hurts more than cannula CVL if already sited √ although infection risk
Left over blood (scavenged)	√ slight concerns about 'leftover'- why extra

	taken?
Population PK	√
Levels available for routine care	√
Sampling windows	√
Other bodily fluids	√
Opt in / opt out & deferred consent	√
Dried blood spots	√
Ratio research: clinical	50:50 i.e. Mon-Fri 9-5 but needs to be more research team – up to 100%
Staffing	Plan sampling to avoid overnight / unsocial hrs staffing Not able offer 24/7 cover
Support	Support staff in clinical areas to participate in research. Workload crucial factor for them
Context	WTCRF √ Wards √ PIC families distressed but got lines in Wards- outpatients- nowhere appropriate
Include all ages	√? palliative an exclusion, healthy children exclude, those that don't adhere to treatment
Priority groups	X
Research feedback	Feedback from research important to families
Care for a patient in a PK study	√

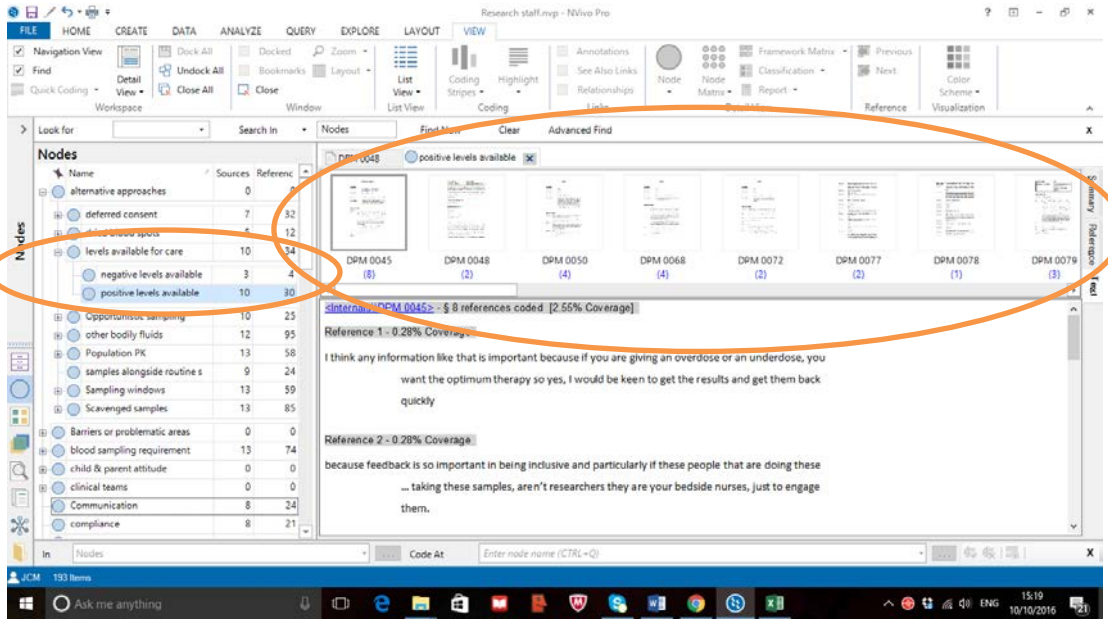
Second stage Magnitudinal coding then took place to review attitudes (where appropriate). In *Figure 71* below each method of alternative approaches to PK studies was classified 'positive' or 'negative' with a frequency count for each.

Figure 71: screenshot of NVivo 11- second line coding with magnitude coding



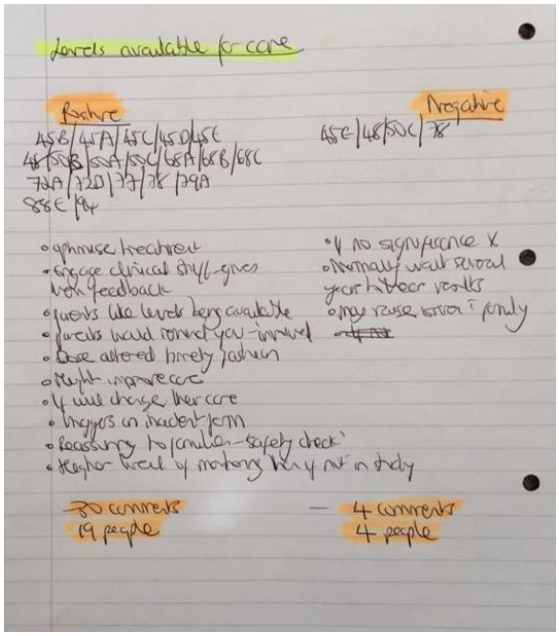
In the screenshot *Figure 72* below 'Levels available for care' is highlighted, i.e. results from PK studies being made available to inform clinical care. This has been sub-coded to 'positive to levels of care'. This features in 10 sources (out of 13 sources) and there were 30 positive comments. The 19 people who stated positive comments are then listed in the side panel of the screenshot and the number below each indicates how many comments they each made. Below this are the comments themselves are listed below. The screenshot is on participants from focus group 45 and some of their quotes are visible in the screenshot.

Figure 72: screenshot of NVivo 11- featuring 'positive' quotes from participants in FG 45



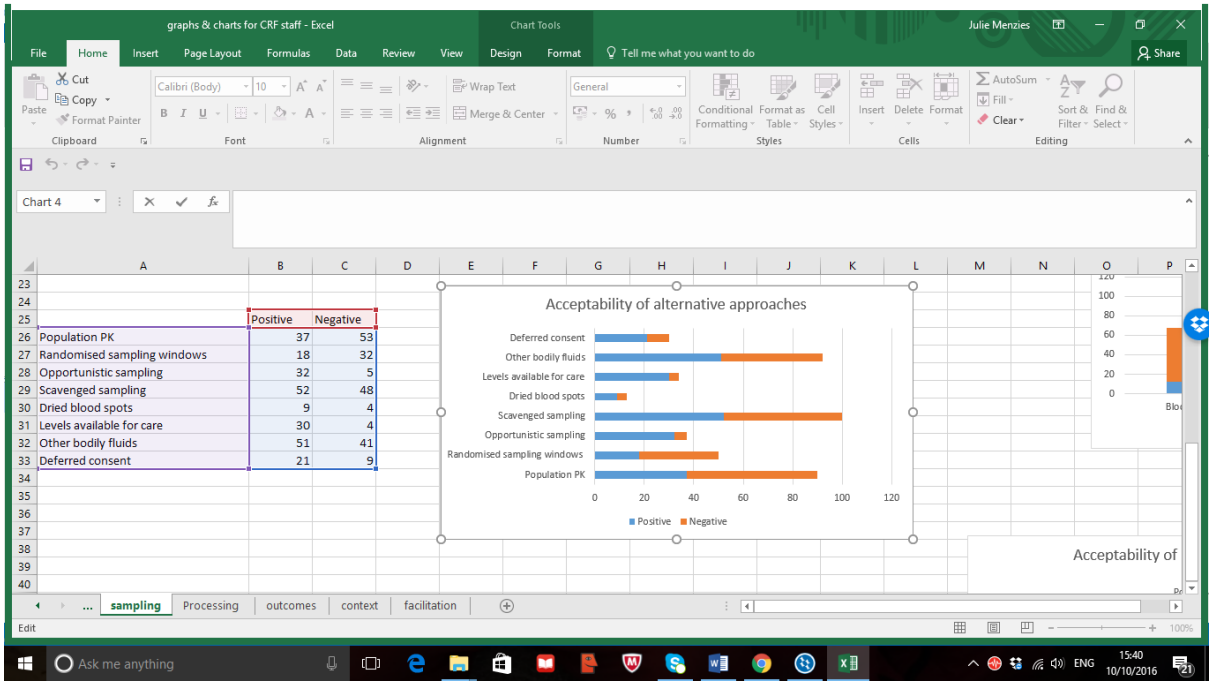
The 19 participants who made 30 positive comments were then transferred onto paper records, with key messages summarised (as in the photograph *Figure 73*).

Figure 73: levels available for care: positive and negative comments



The numerical data was then imported into excel to allow simple descriptive statistics to be calculated (see screenshot *Figure 74*). This shows 'Levels available for care'- 30 positive, 4 negative plotted alongside other strategies to allow comparison in a clustered bar chart.

Figure 74: screenshot of excel and simple quantification of data



	Positive	Negative
Population PK	37	53
Randomised sampling windows	18	32
Opportunistic sampling	32	5
Scavenged sampling	52	48
Dried blood spots	9	4
Levels available for care	30	4
Other bodily fluids	51	41
Deferred consent	21	9

5. Appendix 5: Support algorithm (from Protocol V6.2, 02.04.2014)

If parents experience any distress we will refer to a support algorithm which we have developed:

Step one: is to refer them to a Clinical Nurse Specialist within their area who are often familiar with individual families and their history

Step two: particularly if the situation involves a complaint related to previous care would be to refer them to the Patient Advice and Liaison Service (PALS)

Step three: would be to refer them to the Patient Counselling service within BCH.

6. Appendix 6: Data extraction Sheet for scoping review

Study ID	Reviewer JCM / JM	Country	Author	Publication details (Journal, year, issue, page)
Setting: In hospital: ward, HDU,PICU Outpatient Community				
Study population Inclusion: Exclusion:				
Study design: Phase 1 / 2 RCT: SB/ DB Other:	Study description			
Drug 1	Route of administration IV, IM, Oral, NG, Rectal, Buccal			
Drug 2 (if applicable)				
Type of sample: Blood: Cap / Ven/ Art Urine Other	Schedule:			
PK method:				
Total no. participants:	No. Participants in PK:	No. Participants Included:	Recruitment process described?	
Non-participation: Y /N / Unclear Data loss : Y /N/ Unclear Withdrawal: Y/N / Unclear	Reasons:			
Study meets all final eligibility criteria	Yes No	Reviewers initials	Date	
The following section will be completed by the third reviewer in case of consensus failure between first 2 reviewers: Study meets all final eligibility criteria: Y / N			Reviewers initials: Date:	