Recruitment to clinical trials in adult and child settings: qualitative case study in cystic fibrosis

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ABSTRACT

Empirical evidence indicates that clinical trials are the most challenging type of research where the recruitment of willing volunteers is required. Insights into the process of recruitment are being gained from research examining the perspectives of those individuals directly involved, but there is limited comparative work in this area. Cystic fibrosis (CF), a serious life-long health condition was chosen as a case study for this thesis. It enabled recruitment to be compared across both adult and child settings and from both sides of the exchange. Qualitative interviews were conducted with 82 informants, comprising 20 adult patients, 22 mothers, eight fathers, 12 young people and 20 practitioners, across ten specialist CF centres (five paediatric and five adult). Analysis of transcribed recordings was pluralistic, drawing on elements of grounded theory and discourse analysis.

Findings from this case study indicated that informants were able to make sense of invitations to participate in clinical trials based on personal perceptions of fairness, which could be discerned according to three distinct yet interdependent discourses namely: a rational; a social and a psycho-moral discourse. Rather than a universal ethical principle of fairness, informants made their own judgements of fairness, which took different forms depending on their personal sense of responsibility. Parents acting on behalf of infants and young children focused on doing the right thing and acting in the child's best interest, balancing both parental responsibilities and personal values. Parents of older children focused on negotiating the young person's level of involvement in decisions according to pre-existing family dynamics. Adult patients balanced their own health status, past research experience and personal values to make sense of and respond to the invitation to enter a trial. Practitioners illustrated the delicate balance required for the 'unbiased marketing' of trials, in which they considered their duty of care to patients, inherent trial uncertainty, 'a pressure of numbers' and their own personal values.

In the context of this lifelong condition, recruitment was a social exchange as well as an informational one, in which hope, trust and a sense of moral responsibility were central for informants. Vulnerabilities could arise in relation to these processes, where high hopes could lead to disappointment, a sense of responsibility could lead to obligation, or trust could turn to acquiescence. The findings have implications for enhancing recruitment and raise questions about the appropriateness of generic checklist guidelines for enhancing and supporting the recruitment process. Individuals and families approached about trials want to be part of something of value and to be valued; engaging in what they believe is a worthwhile and fair collaborative endeavour.

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DECLARATION

The material contained in this thesis has not been presented, nor is currently being presented, either wholly or in part for any other degree or qualification.

This thesis is the result of my own work, which has benefited from the advice and support provided by my supervisors, Professor Bridget Young and Professor Ann Jacoby.

CONTENTS

ABSTRACT ..... **i**
ACKNOWLEDGEMENTS ..... **ii**
DECLARATION ..... **iii**
CONTENTS ..... **iv**
LIST OF FIGURES ..... **ix**
LIST OF TABLES ..... **x**
LIST OF APPENDICES ..... **xi**
GLOSSARY OF ABBREVIATIONS ..... **xii**
INTRODUCTION ..... **xiii**
Origin of thesis xiii
Thesis rationale xiii
Clarifying terms xiv
Organisation of the thesis xv
CHAPTER 1: BACKGROUND AND LITERATURE REVIEW **1**
1.0 Introduction 1
1.1 Search strategy 3
1.2 Medicine's prime way of knowing: randomised control trials (RCTs) 5
1.3 Recruitment and accrual 9
1.3.1 Recruitment as an intervention 14
1.4 A discourse on protection and understanding 16
1.4.1 A brief overview and historical origins of informed consent 18
1.4.2 A brief overview of informed consent in children 21
1.4.3 A focus on understanding 24
1.4.4 The therapeutic misconception 26
1.4.5 Hope beyond the 'therapeutic misconception' 28
1.4.6 Limits of informed consent 30
1.5 Altruism: cause for celebration or concern? 33
1.6 Developing a model of trial recruitment 38
1.6.1 A personal balance account 38
1.6.2 Negotiating risk and uncertainty 43

1.6.3 Recruitment as a social act 46
1.7 Summary and positioning my case 53
1.7.1 Paucity in qualitative studies with a comparative focus 54
1.7.2 An underrepresented population 55
1.7.3 A paucity of literature incorporating recruitment from both sides of the exchange 56
CHAPTER 2: METHODOLOGICAL CONSIDERATIONS 58
2.0 Introduction 58
2. 1 Case study and theoretical influences 59
2.1.1 Defining positivism and post-positivism 61
2.1.2 Interpretive paradigms 64
2.1.3 Pragmatism 68
2.2 Positioning my case study 70
2.2.1 The 'case' of cystic fibrosis 73
2.2.2 A qualitative methodology 74
2.3 Quality in qualitative research 76
2.4 Sampling 79
2.5 Analysis 80
2.6 Summary 84
CHAPTER 3: METHODS 85
3.0 Introduction 85
3.1 Research aim and objectives 85
3.2 The research setting 86
3.3 Sampling for semi-structured interviews 88
3.3.1 Sample size 90
3.4 Recruitment to this study 91
3.5 Ethical considerations 92
3.5.1 Approval requirements 92
3.5.2 Service user involvement 93
3.5.3 Risks, burdens and benefits 94
3.5.4 Informed consent 95
3.6 Data collection 96
3.6.1 Multi-perspective qualitative interviewing 96
3.6.2 Development of interview guides 97

3.6.3 Interviewing children and young people 99
3.6.4 Transcription 101
3.7 Ensuring quality 110
3.8 Summary 113
CHAPTER 4: CONTEXT FOR STUDY FINDINGS 114
4.0 Introduction 114
4.1 Details of research setting 114
4.2 Sampling of study informants 116
4.3 Patient and parent sample characteristics 118
4.3.1 Socio-demographic and clinical characteristics 118
4.3.2 Research experience 120
4.4 Practitioner sample characteristics 123
4.5 Details on interview data 124
4.6 Summary 125
CHAPTER 5: FINDINGS 126
WHEN IS A RESEARCH OFFER FAIR? - A RATIONAL DISCOURSE 126
5.0 Introduction 126
5.1 A rational discourse: Weighing things up 127
5.2 The weighing up process: autonomy, responsibility and dependency 129
5.2.1 Autonomy: 'is it worth the risk' 129
5.2.2 Responsibility: 'wanting what's best' 131
5.2.3 Dependency: I can decide but my parents' know best 135
5.3 Information disclosure 138
5.3.1 Patients' and parents' perspectives 138
5.3.2 Practitioners' perspectives 143
5.4 Perspectives on the gold standard 145
5.4.1 Patients' and parents' perspectives 145
5.4.2 Practitioners' perspectives 150
5.5 Rationalising the costs and benefits 155
5.5.1 Patients' perspectives. 155
5.5.2 Rationalising costs and benefits: practitioners' perspectives 164
5.6 Assessing trial burden 168
5.6.1 Patients' perspectives 168

5.6.2 Practitioners' perspectives 173
5.7 Summary 175
CHAPTER 6: FINDINGS 178
WHEN IS A RESEARCH OFFER FAIR? - A SOCIAL DISCOURSE 178
6.0 Introduction 178
6.1 Impact of relationships: patient and family perspectives 178
6.1.1 Familiarity 179
6.1.2 'Feeling comfortable' 181
6.1.3 Feeling valued and being part of something of value 184
6.1.4 Being provided with reassurance 187
6.1.5 Downsides to familiarity 192
6.2 Impact of relationships: practitioners' perspectives 198
6.2.1 Familiarity 198
6.2.2 Right person skills 201
6.2.3 Facilitating a patient's sense of being valued 202
6.2.4 Tailoring and reassurance 203
6.2.5 Downsides to familiarity 205
6.3 Trust and a fair offer: patients' and parents' perspectives 206
6.4 Trust and family relations 211
6.5 Trust and recruitment success: practitioners' perspectives 218
6.6 Summary 222
CHAPTER 7: FINDINGS 224
WHEN IS A RESEARCH OFFER FAIR - A PSYCHO-MORAL DISCOURSE? 224
7.0 Introduction 224
7.1 Patients' and parents' perspectives: a moral discourse 225
7.1.1 Research as a common good 225
7.1.2 A moral responsibility to contribute to a common good 228
7.1.3 A moral education 231
7.1.4 'An inner glow' from contributing to a common good 236
7.1.5 Making sense of saying no: balancing personal interests and responsibility: 239
7.2 Patients' and parents' perspectives: a psychologicaldiscourse 242
7.2.1 'Hoping for the best' 242

7.2.2 'Keeping our spirits up': hope as coping 245
7.2.3. 'Pinning hopes on a cure' 246
7.3 Practitioners' perspectives: a psycho-moral discourse 252
7.3.1 Research as a common good 252
7. 3.2 Why be a recruiter: balancing responsibility and personal interest 255
7.3.3 'The morality of the study' 257
7.3.4 Making sense of recruitment: the morality of marketing 260
7.3.5 A fair selection 266
7.4 Summary 270
CHAPTER 8: DISCUSSION 272
8.0 Introduction 272
8.1 Study Findings 272
8.1.2 A rational discourse: 'weighing things up'. 275
8.1.3 A social discourse: 'feeling comfortable and valued' 277
8.1.4 Psycho-moral discourse: 'Doing my bit and hoping for the best' 279
8.2 Main findings in relation to the existing literature 283
8.2.1 What makes research feel fair: a personal balance account 283
8.2.2 Balancing risk, hope, and a sense of responsibility 285
8.2.3 Recruitment as a social exchange 288
8.3 Potential Vulnerabilities 291
8.3.1 Personal expectations of a trial: a trial as the best option 291
8.3.2 Hope and disappointment in 'wonder drug' trials 293
8.3.3 Trust and acquiesence 296
8.3.4 The 'complexity' of the child setting 298
8.4 Implications of this study 303
8.4.1 Recruitment Policy 304
8.4.2 Recruitment Practice 306
8.5 Strengths and limitations 308
8.6 Future Research 313
8.7 Conclusion 316
BIBLIOGRAPHY 318
APPENDIX 348

LIST OF FIGURES

FIGURE 1.1: Ulrich et al.'s (2012) model of the benefits and burdens of research participation 39

FIGURE 1.2: McCann et al's (2013) conceptual model of factors influencing trial participation 41

FIGURE 1.3: Verheggen's (1998) model of explanation for trial participation 42

FIGURE 1.4: Lengacher's (2001) model for clinical trial participation 51

FIGURE 1.5: Conceptual framework of factors influencing the decision to participate 52

FIGURE 8.1: A conceptual framework of recruitment: judging the fairness of a research offer 274

LIST OF TABLES

TABLE 1.1: Development of search terms for reviewing trial recruitment literature . 4
TABLE 1.2: A range of RCT designs (Jadad, 1998) 6
TABLE 1.3: GCP Guidelines for informed consent (ICH, 1996)..... 20
TABLE 1.4: Misunderstanding in clinical research (Horng, Grady, 2003) 29
TABLE 3.1: The analytic process 103
TABLE 3.2: Identifying common elements: When is a research offer fair? 107
TABLE 4.1 Sampling of specialist CF centres 115
TABLE 4.2: Recruitment of patients and families 117
TABLE 4.3: Recruitment of practitioners 117
TABLE 4.4 Socio-demographic characteristics of the patient/parent informants 120
TABLE 4.5: Research experience 121
TABLE 4.6: Characteristics of practitioner sample 123
TABLE 6.1: The centrality of trust to 'recruitment success' 218

LIST OF APPENDICES

Appendix 1: Examples of electronic searches of databases 350
Appendix 2: Children's Information Leaflet 354
Appendix 3: Topic Guide for Interviewing Parents: 358
Appendix 4: Transcription notation and identification codes 364
Appendix 5: Field Notes 368
Appendix 6: Case Summary 374
Appendix 7: Vignette describing RCT 378

GLOSSARY OF ABBREVIATIONS

CASP	Critical Appraisal Skills Programme
CF	Cystic Fibrosis
CIOMS	Council for International Organisation of Medical Sciences
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTRC	Clinical Trial Research Centre
DoH	Department of Health
EBM	Evidence-Based Medicine
EMA	European Medicines Agency
HTA	Health Technology Assessment
HRA	Health Research Authority
ICH	International Conference on Harmonisation
ICTRP	International Clinical Trial Registry Platform
IOM	Institute of medicine
LRN	Local Research Networks
MCRN	Medicines for Children Research Network
NIH	National Institutes of Health (US)
NIHR	National Institute for Health Research
NSCG	National Specialised Commissioning Group
NWHTMR	North West Hub for Trials Methodology Research
PIC	Patient Identification Centre
RCPCH	Royal College of Paediatricians and Child Health
RCT	Randomised Controlled Trial
SET	Social Exchange Theory
TORPEDO-CF	Trial of Optimal Therapy for Pseudomonas Eradication in Cystic Fibrosis
WMA	World Medical Association
YPAG	Young Persons' Advisory Group

INTRODUCTION

Origin of thesis

This thesis was funded by the Medical Research Council North West Hub for Trials Methodology Research (NWHTMR) based at the University of Liverpool. It forms part of the Patient Perspectives Theme of the Hub, which is aimed at ensuring that the design and conduct of clinical trials are informed by patients' perspectives. I first became involved in this field of research as a qualitative interviewer for the RECRUIT study, which examined processes in recruitment to randomised controlled trial of medicines for children (Shilling et al., 2011). This thesis builds on my prior experience of and interest in clinical trial recruitment.

Thesis rationale

Despite extensive research on clinical trial recruitment, it remains unclear why some trials recruit well and others do not; furthermore there is a distinct lack of theory to unite empirical evidence and direct future research (Sully et al., 2013; Bower et al., 2009; 2014; Campbell et al., 2007). Examining recruitment from multiple perspectives is helping the clinical trials community understand the complexity of the recruitment process (Campbell et al., 2007). Furthermore, multi-perspective qualitative interviewing is an important methodology for understanding the needs, beliefs and experiences of those receiving and providing services (Kendall et al., 2009). In some sense, recruitment to trials could be thought of as a kind of service, forming part of a system meeting a public need, namely to improve healthcare. Nevertheless, qualitative research examining recruitment from both sides of the exchange is less prevalent and there is no qualitative work of this nature comparing adult with child experiences and settings. Comparative qualitative research has

been shown to be a valuable analytical tool for providing theoretical insights into complex social phenomena (Bradley et al., 2007). Furthermore, much of the empirical evidence on trial recruitment is based in oncology with limited work involving individuals with chronic conditions such as cystic fibrosis (CF).

Cystic fibrosis is a genetic disease diagnosed at birth for which treatment requires lifelong, intensive interventions in specialist paediatric and adult CF centres; many of these are research-active presenting an ideal case for examining clinical trial recruitment (Lowton, 2005). At the time my PhD studies commenced, a multicentre phase IV clinical trial (TORPEDO-CF:Trial of Optimal TheRapy for Pseudomonas Eradication in Cystic Fibrosis) was being managed by the Clinical Trials Research Centre (CTRC) in Liverpool.

This trial, which was open to both adults and children, was identified by the Hub management team as a potentially suitable focus to examine current trial experiences in CF. Consequently, a qualitative 'case study' in CF which examined recruitment experiences across adult and paediatric settings, from the perspective of those doing the recruiting and those being recruited, was selected to further current understanding of trial recruitment.

Clarifying terms

The term 'informants' was chosen to refer to all individuals who agreed to take part in this qualitative study, and so distinguish them from people with experiences of clinical trials or other studies, where I use the term 'participant'. Individuals receiving care from specialist paediatric CF centres were referred to as the child sample. This sample was synonymous with the typical definition of a paediatric population which refers to a patient group aged group 0-18 years (Dunne, 2007).

Teenagers with CF typically begin a process of 'transition'[1] to specialist adult CF centres from early teenage years, with most being transferred to adult care by the age of eighteen (Towns & Bell, 2011; Rosen et al., 2003). The oldest child informant in this sample was 17 years old. Children aged seven years and younger who were not invited to take part in this study were described as 'infants'. The remaining child sample was referred to as children, although where relevant I have made further distinctions between a teenager (≥13 years) and the youngest participants (≤9yrs). The term 'patients', was also used collectively to refer to all people with CF, both children and adults who had agreed to take part in this study. The term parents was used to refer to parents of both infants and children with CF. The term 'adults' or 'adult informants' or 'adult patients' was used exclusively to describe adults with CF. The term practitioner was used to describe any health professional who agreed to take part in this study.

Throughout the study, I use the term 'clinical trial' or 'trial' to refer to a randomised controlled trial (RCT). Where I use the term clinical study, I am referring to all other research that does not involve a randomised design. Where I use the term clinical research, I am referring to the collection of clinical studies and trials which require the informed consent of human participants.

Organisation of the thesis

This thesis is divided into eight chapters. In the first chapter, I provide background to the research methodology of clinical trials. This will be followed by a scoping

[1] Transition refers to the 'planned purposeful movement of adolescents and young adults with chronic physical and medical conditions from child-centred to adult orientated health-care systems' (Blum et al., 1993)

review of the structure and extent of knowledge on the subject of trial recruitment. Finally, within this first chapter, I identify key gaps in the literature and explain where my study is positioned.

In the second chapter, I explore the methodological considerations that guided my decision to conduct a qualitative case study in CF. Here I will examine the theoretical orientation of this study and the consequences of this orientation for the methods that follow. In Chapter Three I provide a description of the methods I adopted in this study, describing the process of analysis and interpretation of the findings and including an overview of the conceptual framework upon which the findings will be organised. Chapter Four provides the context for the study findings, detailing the research setting and the sample characteristics. Chapters Five, Six and Seven describe the findings, particularly the main conceptual patterns or discourses identified in informants' accounts of recruitment. These centred on informants' perceptions of the fairness of a research invitation which I grouped according to three thematic patterns or discourses: a rational, a psycho-ethical and a social discourse.

Chapter Five illustrates how informants rationalised research invitations in a deliberate '*weighing up*' of the costs and benefits, assessing how safe or valuable they perceived the trial or study to be; this is interpreted as a form of a rational discourse. Chapter Six illustrated the consequence of trust and the social context on how informants perceived the recruitment process; this is interpreted as a social discourse. Chapter Seven describes how informants' worked to construct a moral and psychological account of their recruitment experience, one in which hope and a sense of duty were most significant. This is interpreted as a form of psycho-ethical discourse. Chapter Eight, provides a summary and discussion of the main findings,

setting them in the context of previous empirical and theoretical work. The implications of these findings in terms of policy and practice, point to areas for future research. Finally, I assess the study's strengths and limitations and provide a brief conclusion.

CHAPTER 1: BACKGROUND AND LITERATURE REVIEW

1.0 Introduction

The most widely used methodology for evaluating the effectiveness of health care involving 'human subjects' is the clinical trial (NIHR, 2015). Without willing participants, clinical trials could not exist, and without an adequate number of appropriately recruited participants, the scientific and ethical integrity of the clinical trial is undermined. The focus of this thesis is to gain insights into the process of recruitment, which is the gateway to trial participation, a process culminating in an individual's decision to participate (Gul & Ali, 2010).

Deciding to participate in a clinical trial requires an individual to make a voluntary, informed choice to expose themselves to uncertain outcomes. Furthermore, the responsibility of recruiting a participant requires a practitioner to invite a patient to consider these uncertainties. Empirical evidence indicates that clinical trials are the most challenging and problematic type of research with respect to recruitment, due to the inherent ethical tension in the conduct of trials surrounding the 'duties to the individuals' versus the 'societal value' of clinical trials (Emanuel et al., 2000; Hellman & Hellman, 1991).

The literature on trial recruitment is vast and diverse, probably reflecting the scale of the challenge in recruiting of sufficient patients to these studies (Campbell et al., 2007; McDonald et al. 2006). Due to the heterogeneity of the literature, compounded by methodological issues, meaningful interpretation of the evidence through systematic reviews has been difficult (Treweek et al., 2013; de Vries et al., 2011; Fayter et al., 2007; Campbell et al., 2007). Furthermore, there is a distinct lack of

'robust theory' to assist in uniting these findings or to guide the direction of trial recruitment research (Bower et al., 2009; 2014; Tramm et al., 2013; Gul & Ali, 2010). Consequently the aim of this thesis is to contribute to the trial recruitment literature, both conceptually and empirically

Therefore in reviewing the literature, as opposed to concentrating solely on 'what works' or what is necessary or 'right' regarding trial recruitment, I will focus primarily on identifying the dominant approaches to researching the topic of recruitment and the consequences of these methods on current knowledge and understanding of the phenomenon of trial recruitment. This review is not intended to be a systematic review of the evidence, but a scoping review of the structure and extent of knowledge on recruitment (Grant & Booth, 2009; Gough et al., 2012). Within this review I aim to reflect the diversity in the empirical evidence whilst identifying literature which has conceptually defined an aspect of trial recruitment or has integrated existing empirical recruitment literature beyond a descriptive level. Therefore the aim of this review is to examine how historical and philosophical assumptions have shaped the direction of recruitment research and the main theoretical insights into this phenomenon and where my research is positioned.

The review was not a 'one-time event' with rigidly pre-defined initial review questions, but rather an ongoing iterative process which extended throughout my PhD studies (Ramalho et al., 2015; Dunne et al., 2011; Charmaz, 2006; 2008). Engaging with the literature prior to undertaking my primary research was essential to position my study within the wider literature and to support my ethics application to conduct empirical work. Nevertheless, owing to my largely inductive approach, I was also mindful of imposing preconceptions and assumptions during

both the literature review and during the process of data analysis. Therefore within my discussion the empirical literature was re-examined more critically in the light of my findings.

1.1 Search strategy

Locating evidence for this scoping review involved a range of strategies, with electronic database searches forming an important component. All the same, I was aware of the limitations of solely relying on database and electronic searches, especially when the focus includes qualitative and theoretical literature where bibliographic databases alone are often not enough (Flemming & Briggs, 2006; Greenhalgh & Peacock, 2005; Shaw et al., 2004). At the outset of my PhD, I was aware of important literature in the field, acquired through previous work in the area of paediatric trial recruitment and I was continually advised about new articles by experts in the field. I also used citation tracking and the screening of article reference lists for relevant literature (Greenhalgh & Peacock, 2005). The database search involved testing and refining various search strategies to balance the sensitivity of the search (number of articles recalled), with the precision of the search (the relevance of the search). As I became more familiar with the labels and terminology surrounding the trial recruitment literature, I developed a series of search terms. These were built on the concepts detailed in *Table 1.1* and involved combining these search terms according to the database and significance of output.

The four main abstract and citation databases I used during the electronic searches included:

i.) MEDLINE (Ovid Medline)
ii.) CINAHL

iii.) PsycINFO
iv.) SCOPUS

Together these databases provided coverage of health sciences, life sciences; physical sciences and social sciences (see Appendix 1 for details of database searches).

TABLE 1.1: Development of search terms for reviewing trial recruitment literature

Word group 1 (recruitment)	Word group 2 (clinical trial)	Word group 3 (Participant)	Word group 4 (health professional)	Word group 5 (perception)	Word group 6 (methodology)
recruit*	clinical trial*	participant*	practitioner*	perce*	qualitative
enrol*	controlled trial*	patient*	doctor*	experienc*	Interview*
particip*	trial*	public	clinician*	understand*	focus groups
declin*	RCT	adult*	physician*	concern*	thematic analysis
'informed consent'	'randomi*ed controlled trial*'	child*	investigator*	view*	narrat*
consent	clinical research	adolescen*	researcher*	perspective*	constant comparative
approach	medical research	people	nurs*	opinion*	interpret*
	research stud*	person	paediatrician*	reason*	grounded theory
		parent*	paediatrician*	account*	ethnograph*
		mother*	GP	motivat*	phenomenolog*
		father*	Professional*	Barrier*	
		prox*		attitude*	
		teenager*		view*	
		consumer			
		layperson*			
		subject*			
		volunteer*			

In addition to searching the above databases, I searched the Cochrane Library, Health Technology Assessment (HTA) NIHR Journal Library, Centre for Reviews and Dissemination, and conducted several other internet based searches. I ran

searches with and without qualitative filters, to examine the extent and diversity of the recruitment literature. No date restriction was applied, and searches revealed that much of the earlier recruitment research was quantitative in design, with much of the qualitative research appearing from the 1990s onwards. Once I had developed search terms which adequately captured the literature, an automatic online search (with Scopus) was also set up, enabling me to identify any new relevant articles to be included outside the main periods of searching. All relevant articles were entered into a bibliographic database (EndNote X7) and grouped according to whether they involved primary evidence, discussion papers, review articles or articles with a theoretical focus. These categories were further subdivided according to the focus of the recruitment research. I only included articles that had been published in peer reviewed journals. Both empirical and review articles were assessed informally, using the relevant critical appraisal tool CASP (2017). For the ethical literature I also included a selection of books.

1.2 Medicine's prime way of knowing: randomised control trials (RCTs)

I will begin this review by examining aspects of the clinical trial design, which are significant to understanding the challenges of trial recruitment. A clinical trial involves a systematic, highly structured, scientific approach embedded in the experimental method, which primarily evaluates treatment effectiveness by comparing outcomes of different treatment groups (Kerr et al., 2006; Jadad, 1998). Reducing potential bias through randomly assigning participants to different treatment groups is the main methodological appeal of this research design (Kerr et al., 2006; Piantadosi, 2005).

The first large scale strictly controlled clinical trial was published by the MRC in 1948 and aimed at establishing the effectiveness of the antibiotic streptomycin for the treatment of tuberculosis (Hill, 1963; Marshall et al.,1948). Carried out during the economic recovery of the post-war period, random allocation was regarded as an ethical way of utilising scarce resources of streptomycin. This trial 'ushered in the new era of medicine' with the RCT becoming 'the model in this field' (Hill, 1963; 1990).

Over the years, multiple types of RCT have been developed, and a range of terms have evolved. *Table 1.2*, while not exhaustive, details some of the different types of RCTs.

TABLE 1.2: A range of RCT designs (Jadad, 1998)

Dimension on which RCTs vary	Examples
RCTs according to the aspects of the intervention they evaluate	Explanatory & pragmatic trial Efficacy & effectiveness trials Phase I, II & III
RCTs according to how participants are exposed to the interventions	Parallel trials Crossover trials Trials with factorial design
RCTs according to the number of participants	From n=1 to mega-trials Fixed size Sequential design
RCTs according to whether the investigators and participants know which intervention is being assessed	Open trials Single blind trial Double blind trials
RCTs according to whether the preferences of non-randomised individuals & participants are taken into account	Zelen design Comprehensive cohort design

Interventions that are evaluated in the context of clinical trials are varied and can include preventative strategies, diagnostic tests, screening programmes and treatments. However, clinical trials are most frequently used to evaluate new drug

treatments. These trials are categorised according to different stages of the evaluation process (Kerr et al., 2006; ICH, 1997). Phase I trials, often referred to as 'first-in-human trials' are conducted after the safety, and potential efficacy of a new drug has been documented in animals. The primary purpose of these trials is the assessment of the tolerance and safety of the drug in humans (Kerr et al., 2006; ICH, 1997). These often involve healthy volunteers who receive a financial incentive, or patients receiving palliative care within oncology or other serious illnesses. Phase I trials involving patients with terminal conditions for which no standard treatment protocol exists are often associated with the characterisation of the 'desperate volunteer' who has nothing to lose (Allmark & Mason, 2006). However, phase I trials are also often evaluating safety with small numbers of participants such as the case of early gene therapy trials in CF. Phase II trials most typically explore therapeutic efficacy, in small groups of patients with a given condition to determine the dose(s) and regimen for phase III trials (Kerr et al., 2006; ICH, 1997). The primary objective of phase III trials is to demonstrate or confirm therapeutic benefit, and these usually involve randomised multi-centred trials involving larger groups of patients (Kerr et al., 2006; ICH, 1997). Phase IV trials are performed after drug approval and include studies that were not considered necessary for approval but are often essential for optimising the drug's use (ICH, 1997).

The randomised controlled trial design has become the 'standard experimental design' or 'gold standard' for determining the efficacy of medical treatments (Grossman & Mackenzie, 2005; Silverman & Chalmers, 1992; Bloom, 1986), to the point where it is often regarded as 'medicine's prime way of knowing' (Oakley, 1999). However paradoxically the process of randomisation - the cornerstone of the clinical trial's scientific appeal - has raised ethical concerns and has been identified as a key reason why RCTs are difficult to recruit to (Miller & Joffe, 2011; Wasserman

et al., 2006; Chard & Ilford, 1998; Lumley & Bastian, 1996). The solution to the dilemma posed by randomisation has been an appeal to the principle of equipoise, which has become the central assumption governing the ethics of randomised controlled trials (Miller & Brody, 2002; 2003). Equipoise is defined as 'the point where a rational, informed person has no preference between two (or more) available treatments' (Lilford & Jackson, 1995). From this position of genuine uncertainty about the relative merits of the treatment options, RCTs are considered to be consistent with practitioners' ethical duties to their patients, as no patient is knowingly given an inferior intervention (Freedman, 1987). Where equipoise is said to exist between two or more given treatments, a person entering a clinical trial of those treatments is likely to be no better or worse off through randomisation than through deliberate recommendation of treatment (Chalmers & Chalmers, 1994).

Whether the concept of equipoise resolves the ethical debates surrounding clinical trials remains contentious, and over the last decade the debates have become increasingly complex and technical (van der Graff & van Delden, 2011; Djulbegovic, 2011; Kukla, 2007). Defining the term itself is challenging and varies according to whose uncertainty is being considered. Uncertainty is considered from the position of the individual practitioner, a community of experts, the individual patient, a community of patients or the public. Consequently debate continues on this subject (Ubel & Silbergleit, 2011; Veatch, 2007; Miller & Brody, 2002;2003 Alderson, 1996).

Nonetheless the RCT has formed the foundation for evidence-based medicine (EBM) which is primarily focused on integrating individual clinical expertise with clinical evidence through systematic research, (Jadad, 1998b; Sackett, et al., 1996). While there are some critics of this approach to medicine and also the clinical trial

(e.g.Carey & Stiles, 2016; Greenhalgh et al, 204 Grossman, 2008; Goldenberg, 2009; Grossman & Mackenzie, 2005; Ashcroft, 2004; Stradling & Davies, 1997) the sheer volume of empirical, theoretical, legislative, institutional, national, and international literature available on the subject clearly demonstrates that clinical trials are perceived as an indispensable component of medicine and clinical research. For example, in 2010 the number of trials recorded in an international trial registry (NIH,ClinicalTrials.gov, 2014) was 101,169, with this figure more than doubling in 2015 to 206,176. Furthermore, disease-orientated health social movements (e.g. HIV, cystic fibrosis and breast cancer), have contributed to a shift in the dynamic between stakeholders in healthcare. (e.g. Hess, 2004; Prior, 2003; DoH, 2008; INVOLVE, 1996; 2017; Feenberg 1992). Many patient and professional organisations are strongly supportive of clinical trials. Providing the opportunity for children and adult patients to benefit from research is now considered an ethical obligation and right. This responsibility is reflected in the continual development of informational resources, trial registries and media campaigns that aim to help patients access and participate in clinical trials e.g. It's OK to Ask' about clinical research campaign (NIHR, 2013),Healthtalk.org, (DIPEx, 2014), International Clinical Trial Registry Platform , ICTRP (WHO 2010).

1.3 Recruitment and accrual

The NIHR has defined recruitment as the 'enrollment of an individual person meeting specific inclusion criteria into a research study' (NIHR, 2015). Trial recruitment is viewed as being successful if a trial recruits to a predefined target sample or beyond within a specified period (Campbell et al., 2007). The process of recruitment has been identified as involving three steps, first identifying eligible participants according to inclusion and exclusion criteria, then approaching them

about the study and finally seeking their agreement and informed consent to join the study (Preston et al., 2016). Generally, a patient's clinician must provide the infrastructure for recruitment, by agreeing that their centre will participate in the trial and by providing appropriate access to patients. Consequently, conceptions of recruitment have extended to include a clinician's agreement to participate in the trial in principle (Bower et al., 2009). Trial recruitment has also been positioned within a broader conceptual framework which extends beyond the perspective of patient and the recruiter, to include the 'strategic 'proactive' management of trials (Menon et al, 2008; Francis et al; 2007; Campbell et al, 2007; Walson, 1999; Farrell, 1998). This focus on the importance of trial management has lead to the development of a tentative 'business model approach' of the trial process. According to this model, recruitment is viewed as having 'market segments' which includes recruiting the support or 'buy in' of 'active sponsors' clinical teams and 'opinion leaders' (Campbell et al., 2007). Nonetheless, more commonly within the literature, the term recruitment is used to refer to the role of practitioners in 'offering patients the opportunity to take part in a trial' (Rendell et al., 2007) which is the focus of this review and my subsequent research objective.

Adequate accrual or recruitment is necessary to uphold the scientific merit of trial methodology, as it is heavily dependent on statistical inferences which require certain sample sizes (Ashcroft, 2004; Warlow, 2002). Clinical trials, therefore, need to be able to meet their recruitment targets, which concern the number of patients required to make the study feasible (NIHR, 2015). Inadequate recruitment leads to samples being smaller than planned, with reductions in statistical power necessary to detect potentially important clinical differences and less precise estimates of treatment effects (Warlow, 2002). Moreover, it may be necessary to extend a trial to reach the required sample size, which as well as increasing costs, results in delays in

extending the findings to clinical practice, fewer trials being conducted overall and consequently reduced availability of evidence to inform patient care (Campbell et al., 2007). This scientific concern of adequate accrual is therefore also an ethical concern relating to the effective use of health care resources.

A significant proportion of clinical trials fail to achieve their planned recruitment targets for reasons that are not well understood (Sully et al., 2013; Treweek et al., 2010; Campbell et al., 2007). Inadequate recruitment, whether of adults or children, is one of the principal reasons for trial failure (Sully et al., 2013; McDonald et al., 2006 et al., Prescott et al, 1999) and has a major impact on the value of findings, the costs and the workload of trials.

In response to this ongoing challenge of 'poor recruitment' an extensive, diverse and ever-growing evidence base has emerged, centred on improving recruitment rates to clinical trials, by identifying factors which may impact on them. A significant proportion of this research has examined dimensions of the recruitment process as perceived by the patients or recruiting clinician, to identify 'barriers' or 'facilitators' to successful recruitment. Surveys and interviews have investigated the views of clinicians, adult patients and children and their families, across a range of contexts (Luchtenberg et al., 2015; Peeters et al., 2012; Lazovski et al., 2009; Sharp et al. 2006; Caldwell et al., 2002). Much of the evidence has been synthesized into numerous reviews (e.g. Tromp et al 2016; Sully et al, 2013; Rendell et al, 2007; Campbell, 2007; Mills et al., 2006; Fayter et al 2006; Prescott et al, 1999; Lovato et al., 1997; Hunninghake et al., 1987).

With regards to clinicians' perceptions of the factors influencing recruitment success, some consistent features have been identified including; time constraints,

resource and role issues, concerns with information and consent as well as the importance of the research questions (Fayter et al., 2007; Rendell et al., 2007). Repeated evidence is also found of the potential for the clinician to present a barrier to patient participation through their position as gatekeepers to trials (Prescott et al., 1999; Lavato et al., 1997; Fayter et al., 2007). Nevertheless, by far the most prominent finding is the multi-dimensional nature of practitioner identified factors, in which a collection of numerous issues have been identified as having the potential to influence recruitment (Fayter et al., 2007; Rendell et al., 2007).

Factors that can influence trial recruitment as perceived by adults and children and parents have also been identified. Prominent among these is trial burden, including physical risk and inconvenience, and concerns about trial uncertainty (Tromp et al., 2016; Meropol et al., 2007; Abraham et al., 2006; Ross et al., 1999). For adults and parents, a preference for a particular treatment (or no treatment) is also prominent in the literature (Mills et al., 2011; King et al., 2005). The most prominent personal motivators as perceived by adults, children and parents include hope for a personal health benefit, contributing to science and helping others (e.g. Dobson et al., 2015; Ulrich et al., 2012; Fry & Dwyer, 2001; Broome et al., 2001; Jenkins & Fallowfield, 2000). Nevertheless, consistent with practitioners' findings, the multidimensional nature of participants' and relatives' motives for trial participation is the most prominent feature of the literature (Tromp et al., 2016; Ulrich et al., 2012; Truong et al., 2011).

Much of this evidence is based on quantitative methodology involving attitudinal surveys administered to patients, parents of children or practitioners, or exploration of their views of hypothetical trial scenarios (Brody et al., 2005; Schron et al. 1997; Henzlova et al., 1994). Consequently, there is a concern that using limited

predefined fixed response formats, or hypothetical trial scenarios may bear little resemblance to how trial recruitment is actually experienced (Fayter et al., 2007). Moreover, methodological weakness within many of the studies combined with the striking heterogeneity across studies has made a meaningful interpretation of these findings problematic (Fayter et al., 2007; Rendell et al., 2007). This existing literature has been described as painting 'a mixed and uncertain picture' (Ulrich et al., 2012). Also, a large body of this evidence exists in the field of oncology, particularly in the context of paediatric trials. Therefore there is a concern that issues relevant to this setting may not apply to other settings or patient groups (Tramm et al., 2013). These findings indicate the complexity of trial recruitment, which is further complicated by few authors dealing with 'the issue holistically' or conceptually (Gul & Ali, 2010).

In-depth qualitative approaches have provided further insights (McCann et al., 2013; O'Cathain et al., 2013; Fisher et al., 2011; Campbell et al., 2007; Donovan et al., 2002; Broome et al., 2001) and these approaches are increasingly being used to elucidate detailed knowledge of potential facilitators and barriers from the perspective of those doing the recruiting and those being recruited, across child and adult settings (Mills et al., 2011; Shilling et al., 2011; Madsen et al., 2007; Salmon et al., 2007). This evidence has indicated important differences between how some practitioners, compared to children and parents perceive the process of recruitment (Shilling et al., 2011). Qualitative evidence has also provided insights into the underlying mechanisms with regards to the barrier of time for practitioners (Salmon et al., 2007) and led to the reconceptualisition of trial treatment preferences from a barrier to an integral part of the information exchange (Mills et al., 2011). A move from the ethical ideal of promoting autonomy to one that emphasises the 'loneliness of autonomy', the importance of relational aspects of recruitment and the centrality of trust has also arisen from qualitative work (Madsen et al., 2007).

Furthermore, reviews focusing on qualitative empirical evidence examining the determinants of recruitment according to patients' demographic characteristics and trials targeting particular health contexts (e.g. Hughes-Morley et al., 2015; Limkakeng et al., 2013; Tooher et al., 2008) are helping to identify areas which may require special consideration during the recruitment process. For instance, issues around confidentiality and 'social discrimination' in HIV trials (Mills et al., 2006), issues of timing and method in maternal and perinatal trials (Tooher et al., 2008) or sensitivity to perceptions of 'stigma' in trials recruiting individuals with depression (Hughes-Morley et al., 2015).

Within the family context, when a child is considered old enough to have an opinion, issues around managing differing preferences of the involved parties are being identified as key. (Madden et al., 2016; Snethen et al., 2006; Broome & Richards, 2003; Olechnowicz et al., 2002). Nevertheless, there remains a need for further qualitative research extending to diverse populations which are currently underrepresented in the evidence-base particularly in the context of chronic illnesses such as CF. At the time of submitting my proposal for ethical review; I identified one qualitative study examining motivations for clinical research participation amongst adults with CF (Lowton, 2005). A further qualitative study examining how young people with CF understand their research experience was identified during a later search (Dobson et al., 2015). Both studies support the observation that recruitment literature in the context of CF is scarce (Tromp et al., 2016; Dobson et al., 2015; Lowton, 2005).

1.3.1 Recruitment as an intervention

Dovetailed with the literature examining factors that influence recruitment, is an overlapping set of evidence focused on assessing the effectiveness of 'recruitment

strategies' to overcome identified barriers and to promote recruitment (Rick et al., 2014; Treweek et al., 2010; Caldwell et al., 2010; Bower et al., 2009; Campbell et al., 2007; Watson & Torgerson 2006; McDaid et al., 2006). This evidence base lends itself to viewing recruitment as a type of 'intervention' or strategy to be tested for effectiveness. Recruitment strategies involve any intervention that is aimed at improving recruitment rates to a clinical trial and may be directed at potential participants, clinicians or the management of the overall trial (Raynor et al., 2009; Campbell et al., 2007; Embi et al., 2005).

The most robust test of the effectiveness of a recruitment method is considered to be a randomised controlled trial, comparing one recruitment method with an alternative method 'nested' within an ongoing treatment intervention trial (Bower et al., 2014; Treweek et al., 2013). So in effect, this methodology constitutes a trial within a trial. While this approach is viewed as the most 'scientific', it faces the same potential barriers as all trials, for instance, a practitioner may have a preferred recruitment strategy and have concerns about the effectiveness of the proposed strategy (Bower et al., 2009). Other approaches aimed at improving recruitment rates evident across the literature include detailed examination and adaptation of the trial process and recruitment strategies in ongoing trials and a rise in feasibility and development studies (Hoddinott, 2015; Menon et al., 2008; Campbell et al., 2007; Vollmer et al., 1992). For example, Kaur and colleagues (2012) have devised a survey tool based on the current evidence base on barriers and facilitators to trial recruitment. This tool has been proposed as a method to establish the recruitment experiences of clinical teams in order to gain relevant information to assess, monitor and improve recruitment, either during an ongoing trial or for future trials.

Interventions to improve recruitment have also been the focus of ongoing reviews (Preston et al., 2016; Treweek et al., 2010; 2013; Caldwell et al., 2010). These reviews have shown some strategies to be effective in improving recruitment rates to trials, including telephone reminders to non-respondents, use of opt-out rather than opt-in procedures for contacting potential participants and the use of open designs where participants know which treatments they are going to receive in the trial (Treweek et al. 2010;2013). Having a dedicated trial manager and making a specific member of staff responsible for recruiting participants has also been shown to be associated with recruitment success (Campbell et al., 2007; Preston et al., 2016). Nevertheless, the widespread and often disparate evidence has made conclusive interpretations difficult, with the effectiveness of many strategies remaining unclear (Bower et al., 2014; Treweek et al., 2010). Furthermore, gaining an understanding as to why recruitment to a trial is successful appears too complex to be understood by any one type of evidence alone and requires other components (Hughes-Morley et al., 2015; Bower et al., 2014; Campbell et al., 2007). Qualitative methods 'nested' within clinical trials have been used to provide further insights into the recruitment process and have also led to the development of complex interventions and frameworks for good recruitment practice aimed at improving recruitment rates (Realpe et al., 2016; Donovan et al., 2002; 2009; 2014). However, in the absence of a unified theoretical framework informing recruitment, translating these findings into generalisable impacts on the recruitment process is difficult (Bower et al., 2014).

1.4 A discourse on protection and understanding

While the collective impact of clinical trials on the advancement of medical knowledge is undisputed, it cannot be assumed that all clinical trials are intrinsically of value or inherently good. The research infrastructure which has

evolved to support and promote the effective implementation of clinical trials equally evolved to protect participants from harmful poor quality research. Consequently, there are two interrelated discourses, one that primarily focuses on achieving recruitment targets regarding adequate 'accrual', and another focused on strengthening the ethical conduct of recruitment in terms of protecting participants from harm. At the heart of this protection discourse is the principal legal instrument in the regulation of clinical research - informed consent, aimed at protecting the rights and welfare of 'human subjects' (WMA, 2013; Bowling, 2009).

Whatever way recruitment is defined, successful recruitment usually involves obtaining informed consent, and the informed consent process cannot begin without the process of recruitment. There are some key exceptions, for example, certain types of cluster trials[2] and trials of emergency treatments (Woolfall et al., 2014; Sim & Dawson, 2012). Nevertheless, for the most part, informed consent is regarded as an essential ethical and legal requirement in clinical research. Consequently, the discourse on informed consent needs to be considered with regard to understanding what is known about trial recruitment. The literature on informed consent is extensive, complicated and highly debated (Corrigan et al., 2009; Manson & O'Neill, 2007).

Informed consent is centred on the ethical principle of respect for autonomy which is believed to be upheld by ensuring a patient makes their own decision (Mason et al., 2013). An individual's consent must usually be obtained before a research treatment is given and the person consenting must have the capacity to make the

[2] In cluster randomised controlled trials the intervention is randomised at the group level (e.g. village, hospital, school) rather than the individual patient, making obtaining consent at the individual level unattainable in certain circumstances (Sim & Dawson,2012)

decision (Beauchamp & Childress, 2013). This decision has been defined as the giving of voluntary permission by an individual who has been informed, in language they understand, about the risks and benefits of the proposed research (Beauchamp & Childress, 2013; Mason et al., 2013).

1.4.1 A brief overview and historical origins of informed consent

To fully appreciate the impetus for and significance of this bioethical discourse on protection, it is necessary to briefly trace the historical origins of informed consent. The evolution of informed consent and the regulation of clinical research to protect vulnerable research subjects from harm has a complex and tragic history dominated by abuse and research failings involving both adults and children (Beecher, 1966; Brandt, 1978). Focal points in this regulatory discourse typically include Nazi human experimentation during World War II (Thieren & Mauron, 2007; Brandt, 1978) and the non-treatment of individuals with syphilis in the Tuskegee study.

A pivotal point in this history was the creation of the first internationally agreed standard - the 1949 Nuremberg Code – produced following World War II, which set the boundaries for 'permissible experiments' on human subjects. The Nuremberg standards were then developed in the Declaration of Helsinki in 1964, which has become the most influential international statement on ethical principles for medical research, now on its ninth revision (WMA, 1964; 2013). This set of principles not only requires that the clinician/researcher protects the welfare of the 'human subject' and ensures the scientific integrity of the 'experiment', but also establishes that subjects can actively protect themselves with the 'absolutely essential' requirement of 'voluntary consent' and the 'liberty to bring the experiment to an end' (Shuster, 1997).

This early legislation borne out of a responsibility for protection of research participants has paved the way for the current intricate array of International, European and National guidelines and legislation, which is continually being updated and amended to reflect the changing environment (e.g. CIOMS, 2016; NHS; HRA, 2014; Regulation (EU) No 536/2014 on Clinical Trials on Medicinal Products for Human Use; DoH, 2009; UK Medicines for Human Use Clinical Trials Regulation, 2004; ICH (E6) Guidelines for Good Clinical Practice, 1996).

While the emphasis on regulation and protection has remained, the excessive burden of legislation has also emerged as a growing concern amongst both patients and professionals (Feenberg, 1992). Research ethics committees have increasingly come to regard their focal duty as attending to the adequacy of the informed consent process (Corrigan et al., 2009). However, more recent research failings including: i) the death of Jesse Gelsinger in the US, 1999,the first person publicly identified as having died in a clinical trial for gene therapy (Jenks, 2000); ii) the Alder Hey inquiry, involving the unauthorised removal and retention of paediatric organs following post-mortem (Redfern et al., 2001; Hall, 2001; Burton & Wells, 2001) and, iii) the life-changing side-effects experienced by healthy volunteers in a phase I trial (trial TGN1412) at Northwick Park hospital (Goodyear, 2006; Attarwala, 2010) has sustained an emphasis on the adequacy of the informed consent process, with the hope that this focus will better protect research participants from potential harm (Corrigan et al., 2009). As a result, the doctrine of informed consent in clinical research is far-reaching, with extensive attention to procedural detail an essential legal and ethical prerequisite for almost all research involving human subjects (Boulton & Parker, 2007). Below *(Table 1.3)* is the information a practitioner is legally and ethically required to share, during the recruitment process for a clinical trial,

according to the Good Clinical Practice Guidelines (GCP) that were in place at the time of data collection for this study (ICH Working Group, 1996).

TABLE 1.3: GCP Guidelines for informed consent (ICH, 1996)

Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

(a) That the trial involves research.
(b) The purpose of the trial.
(c) The trial treatment(s) and the probability for random assignment to each treatment.
(d) The trial procedures to be followed, including all invasive procedures.
(e) The subject's responsibilities.
(f) Those aspects of the trial that are experimental.
(g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
(h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
(i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
(j) The compensation and treatment available to the subject in the event of trial-related injury.
(k) The anticipated prorated payment, if any, to the subject for participating in the trial.
(l) The anticipated expenses, if any, to the subject for participating in the trial.
(m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
(n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the 16 Guideline for Good Clinical Practice applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
(o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
(p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
(q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
(r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
(s) The expected duration of the subject's participation in the trial.
(t) The approximate number of subjects involved in the trial.

1.4.2 A brief overview of informed consent in children

A further complexity to the regulatory discourse on clinical trials is the case of the 'therapeutic orphan' in which, following the introduction of standards to protect 'human subjects', children were largely excluded from research. Early research regulation for human 'subjects' (Nuremberg code, 1949) viewed research as a potential harm, from which vulnerable people should be protected, and children were therefore often deemed inappropriate candidates for research (Kanner et al., 2004; Steinbeck, 2002).

Literature concerning the ethical tensions inherent in clinical research involving children is extensive and contentious, spanning many decades (e.g. Nuffield Council on Biethics, 2015; Laventhal et al., 2012; Alderson, 2007; Diekema, Stapleton, 2006; Edwards & McNamee, 2005). Integral to this tension is the construction of childhood as 'a vulnerable formative time' with the duty to protect more apparent, and the balancing of harms and benefits more complex than within the adult context (Sammons & Starkey, 2012; MRC, 2004). In addition, commercial paediatric trials were regarded as having an insufficient return on investments, with priorities being adult-focused, due to the greater burden of disease in adults, combined with a lack of legal enforcement for paediatric versions of drugs (Klassen et al., 2008; Dunn, 2007).

Clinical experience has shown that due to developmental and physiological differences between adults and children, children may be exposed to serious unintended harms from medications without high-quality paediatric trial evidence (Klassen et al., 2008; 2009; Kearns et al., 2003; Caldwell, 2004). Furthermore, the potential of paediatric research to address the growing burden of non-communicable chronic adult diseases that have their origins in childhood has also

been increasingly recognised (McIntosh et al., 2000). The case of cystic fibrosis is an example where the research on the paediatric population is particularly valuable, given that survival for many patients now extends well into adulthood. As the understanding of the pathology of the disease develops over time, early intervention, combined with the continued development of safer more efficacious drugs, has been identified as critical for the improved management of the condition over the patient's lifetime (Pinxten et al., 2011).

Increasing realisation of the necessity of paediatric research, combined with the growing influence of EBM, led to changes in legislation, with a requirement to increase the number of paediatric trials (Pinxten et al., 2009; 2011). Ethical concerns about children participating in clinical trials have not gone away, but they have been outweighed by concerns about denying children access to properly tested medicines (Dunne, 2007). However, paediatric trials are subject to tighter regulation and a more stringent risk-benefit ratio, reflecting children's special status (Van't Hoff & Offringa, 2015; Modi et al., 2014; Wendler et al., 2005; MRC, 2004; McIntosh et al., 2000; Smyth & Weindling 1999).

Whether children should be viewed as vulnerable per se, has however been questioned. Viewing particular groups such as children as vulnerable fails to capture the diversity within the group or the reasons why these individuals may be at increased risk of harm (Nuffield Council on Bioethics, 2015). Nevertheless, children are still widely regarded as being *potentially* vulnerable in the research context, warranting extra protection compared to adults (Nuffield Council on Bioethics, 2015; Neill, 2005; MRC, 2004). An important modification in the informed consent process in children's trials requires that a parent or legal guardian consent on the child's behalf and that the child is involved in the decision via some form of

assent process, where they are able. The requirement of a parent or legal guardian's permission is viewed as a way of ensuring a child's interests are protected as it is assumed that these individuals will make a decision in the child's best interest (Diekema & Stapleton, 2006). The latest amendment of the Declaration of Helsinki (2013) states:

> *'When a potential research subject who is deemed incapable of giving consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.*

Nonetheless, the paediatric regulatory research framework is complicated by how researchers deem whether a child is capable of consent or assent, and the intricate, convoluted legislative system governing research involving children, which is influenced by two legal systems, the trial regulatory system and the common law (Nuffield Council on Bioethics, 2015). In the context of clinical trials of investigational medicinal products (CTIMPs), a person under the age of 16 is unable by law to give informed consent to participate in a clinical trial. A CTIMP involves a clinical study aimed at determining the safety or efficacy of a medicine, foodstuff, or placebo in humans as defined by the Medicines for Human Use (Clinical Trials) Regulation (2004, 2014). Within clinical research outside the context of a CTIMP, the common law applies in which young people aged between 16 and 18 are presumed to be competent to give consent (MRC, 2004). In addition, children under 16 can decide for themselves whether they wish to take part in a particular study if they are considered to have capacity (Nuffield Council on Bioethics, 2015)

The informed consent process in the paediatric context is therefore considered complex (Shilling et al, 2009.,Prichard-Jones et al, 2008; Cadwell et al.,2003;2004; Olechnowicz et al., 2002; Miller & Kenny, 2002). However the underlying principle of all current guidelines is that a child should be included in the process as far as possible and in accordance with their individual preferences i.e. children don't have to be involved in the decision if they don't want to be (Nuffield Council on Bioethics, 2015; Smyth & Weindling, 1999).

1.4.3 A focus on understanding

In addition to the broad discourse of protection surrounding research, the clinical trial design has its own set of inherent ethical tensions**.** Allowing treatments to be randomly allocated by 'chance' has been described as a deviation from culturally accepted moral norms in healthcare (Lantos, 1994). Making decisions about trial participation is different to making decisions about clinical care outside of trials. Trials confront patients with a level of uncertainty. Such uncertainty is less prominent in routine (therapeutic) clinical care, where the practitioner would typically recommend a standard treatment, and for which there is a likelihood that the patient will benefit. In trials, where the primary objective is generalisable scientific knowledge, the prospects of individual therapeutic benefits are typically unknown, ranging from exploratory (phase 1 trial) to uncertain benefits (phase 3 trials) (Dupont et al., 2016; Edwards et al., 1998). Consequently, the most widely cited ethical concern with regards to clinical trials is that patients 'sacrifice themselves for the benefit of future patients by participating in clinical trials' (Friedman et al., 2012; Glass et al., 2006; Afshar et al., 2005; Sharav, 2003; Edwards et al., 1998).

From the perspective of the practitioner, trials introduce a tension between the duty to produce generalisable scientific knowledge, and the duty of care to provide optimal individualised care (Kopelman, 1986; Gifford, 1986). The practitioner is ethically obligated to view patients as more than a means to an end, even if the end is for the benefit of future patients (Lantos, 1994). The primary concern, therefore, is whether the practitioner must sacrifice the goal of individualised best treatment, for statistical efficiency (Schaffner, 1986).

While a position of clinical equipoise remains integral to upholding the scientific and ethical integrity of a trial, the main focus of the literature with regards to countering such ethical tensions has been on upholding the requirements of the informed consent process. The most frequently cited requirement for policies regarding informed consent in the research context is that the potential participants understand the nature of the study to which they are consenting (Beauchamp & Childress, 2013; Dawson, 2009). This predominant view of informed consent is often understood in terms of rational-choice theory which is regarded by many as a normative model of decision-making (Hardman, 2009; Corrigan, 2003; Weinfurt, 2004). In the context of a clinical trial this position presupposes that if a competent individual is provided with accurate, adequate information about the trial, they will be able to make a rational decision in their own best interests (Alderson & Goodey, 1998; Corrigan, 2003; Weinfurt 2004). Consequently, a significant proportion of empirical evidence has focused on the provision of information, and on individuals' understanding and recall of the ethical and legal requirements of informed consent, to ensure the protection of the participant from harm and protection of sponsors from litigation. (e.g. Hunfield & Passchier, 2012; Gammelgaard et al., 2004; Kodish et al., 2004; Lynoe et al., 1991) .

This literature is extensive, examining information provision from the perspectives of children, parents, adults and practitioners and focusing on issues such as competency, understanding, knowledge and communication. This body of work includes research examining methods of obtaining informed consent in real trials (Hutchinson et al 2007;Allmark & Mason, 2006) and in hypothetical trials (Jeste et al 2009; Llewellyn-Thomas et al; 1995), and the quality of the communication process (Brown et al 2004; Fallowfield et al 2002) and of information leaflets (Barnett et al, 2005). The effectiveness of strategies to explain abstract concepts of trial design have also been examined including randomisation and equipoise (Kerr et al., 2004; Mills et al., 2003; Jenkins et al., 2002). Standardised measures to assess the competency and capacity of adults and of children's ability to understand key dimensions of the informed consent process have been developed as a means of assessing and strengthening the ethical conduct of clinical trials (e.g. Hein et al., 2012; 2015; Joffe et al., 2001; Appelbaum & Grisso, 2004). Within this work on protection and understanding, an important theoretical construct has emerged - the therapeutic misconception, in which patients are believed to be susceptible to conflating the aims of clinical care with the aims of research. This construct has further reinforced and sustained the focus on protection of participants through ensuring their 'understanding' of research.

1.4.4 The therapeutic misconception

The therapeutic misconception is believed to occur on two key dimensions: i) an incorrect belief that individual needs will determine treatment assignment and; ii) an overestimation of the likely benefits of entry onto clinical trials during randomisation (Appelbaum et al., 2012; Miller & Joffe, 2006; Joffe, 2006; Lidz et al., 2002). The therapeutic misconception has also been applied to participants' appreciation of risk, in which evidence indicates that patients often agree to take

part in clinical trials with 'only the most modest appreciation of risk' (Lidz et al., 2004). This concept was first described by Appelbaum and colleagues (1982) as a patient's assumption that within a clinical research context, decisions about their clinical care will be made solely with their personal therapeutic benefit in mind.

The 1982 article which first proposed the therapeutic misconception was based on two psychiatric 3-arm placebo controlled trials. Project A, involved a social skills training programme and project B involved psychotropic medication. Within project A the informed consent document did not contain details of how an individual's treatment was to be allocated i.e. by randomisation, and this information was also routinely omitted during oral consent interviews. Under these conditions, where patients were unclear about how treatment was decided, many constructed therapeutic accounts of treatment allocation. That is patients assumed that their treatment was decided according to what was clinically best for them. It is arguable, where no account of treatment allocation was given to patients, whether this evidence supports' a 'misconception', as an individual cannot misconceive something they are not told in the first place. In contrast in project B all individuals underwent a nearly ideal consent process in which the method of allocation was discussed at length, but only 8 out of 18 patients understood that the assignment would be random and 6 believed that the trial would have a therapeutic basis, thus lending support to the notion of a therapeutic misconception.

In later work, Appelbaum and colleagues stated the importance of distinguishing between the therapeutic misconception and a mere lack of understanding on the part of the patient (Appelbaum et al., 2004; Lidz et al., 2002). For instance, a patient may fully understand the nature and purpose of the study yet still attribute therapeutic intent to the study and the converse may also be true. This suggests that

the therapeutic misconception is at least in part personally motivated as opposed to being simply the result of a misunderstanding. Healthcare norms relating to the doctor-patient relationship and an individual's past health care experiences are believed to be the source of the therapeutic misconception, leading patients to confuse the goals of research with those of treatment (Lidz et al., 2002).

Despite extensive research examining the most effective ways to communicate about trial participation and risk to maximise understanding, the therapeutic misconception remains pervasive (Appelbaum et al., 2008; 2012). This concept is especially prominent in phase 1 oncology trials, which are not expected to provide any therapeutic benefits and an individual's fear of death and hope for cure or remission are apparent (e.g. Pentz et al., 2012; Daughtery et al., 1995; 1999). Nonetheless, the therapeutic misconception has been described in diverse populations extending beyond oncology trials and including adults, parents and children and practitioners across a range of health contexts (e.g. Tromp et al., 2016; Snowdon et al., 2006; Vitello et al., 2005; Gammelgaard et al., 2004).

1.4.5 Hope beyond the 'therapeutic misconception'

The predominant discourse on the therapeutic misconception has focused on the accurate provision and understanding of trial information. However, researchers have questioned a purely information processing perspective of the therapeutic misconception, where an unrealistic hope for personal benefit is viewed as no more than a 'false belief' or misunderstanding (Weinfurt, 2004). Consequently, interpretations of the therapeutic misconception have been continually redefined potentially highlighting the underlying complexity of the concept (Snowdon et al., 2007; Kimmelman, 2007; Sugarman et al., 2005). Horng and Grady (2003) have

reformulated the therapeutic misconception to include a continuum of hope according to how adaptive or inaccurate an individual's hope for personal benefit is perceived to be *(Table 1.4).*

TABLE 1.4: Misunderstanding in clinical research (Horng, Grady, 2003)

Concept	Definition	Ethical significance	Example
Therapeutic misconception	The research subject conflates research & care	Rarely tolerable because understanding the nature of research is necessary for an autonomous decision.	*Mark believes that the purpose of the phase 1 cancer trial is to help him personally*
Therapeutic misestimation	The research subject underestimates risk, overestimates benefits or both.	Sometimes tolerable because understanding the exact probability of harm and benefit may not be necessary for an autonomous decision to participate	*Susan estimates that she has a 30% chance of benefit in the Phase 1 cancer trial. A meta-analysis of a similar study shows that the benefit accrues to 5% if subjects.*
Therapeutic Optimism	The research subject hopes for the best personal outcome	Always tolerable because hope does not always compromise the autonomy of a decision to participate in research.	*Thomas hopes that he will be one of the 5% who benefits from the phase 1 cancer trial.*

Based on in-depth examination of hope in the context of early phase oncology trials, Cox (2002) views hope as a complex multi-dimensional concept that can only be fully understood through an interpretative approach (Cox, 2002). Weinfurt (2004) has argued that interpretations of the therapeutic misconception vary according to a researcher's theoretical orientation. From a discursive perspective, he proposes that patients reporting high expectations can provide alternative interpretations beyond indicators of misunderstanding. Discursive psychology treats talk as social action and from this position Weinfurt (2004) considers that a chosen discourse or activity may be undertaken by individuals to achieve specific aims, which may have multiple goals. For example, an individual may choose to describe high expectations or 'false belief' or 'misconceptions' to provide comfort to loved ones, to generate

positive thinking or as an expression of confidence in care givers (Weinfurt, 2004). However, it remains unclear where healthy optimism ends, and a potentially deleterious misunderstanding begins. Nevertheless, whichever way the therapeutic misconception is defined and understood the construct of hope remains inextricably linked to this concept. Horng and Grady's (2003) account appears to provide some way to bridging these diverging views *(Table 1.4)*

1.4.6 Limits of informed consent

This literature on the therapeutic misconception has sustained much empirical research examining the provision and understanding of information. It has also highlighted the 'unattainability' of the comprehension interpretation of informed consent (Dawson, 2009; Corrigan et al., 2009). Over 30 years of empirical evidence demonstrates substantive problems in realising informed consent in the context of clinical trials (Dawson, 2009).

To explore conceptions of rationality in a clinical trial from the perspective of patients and researchers, Djulbegovic & Hozo (2012) employed a trust version of the Prisoner's Dilemma, a widely used example in game theory. Game theory comprises a mathematical discipline, which forms part of the broader group of rational choice theories for describing and analysing interactive decision-making (Hardman, 2009). Researchers have used game theory as an analytical tool to understand social interactions and make predictions about how a rational individual would behave, including in medical consultations (Tarrant et al., 2004).

Aware of the often fraught, conflicting interests typical in trial recruitment Djulbegovic & Hozo (2012) used this mathematical model, to address the question

when is it more rational not to cooperate versus cooperate in the context of a clinical trial. Under the assumptions of this mathematical model, they reported the 'disconcerting' finding that trial participation was a rational strategy meeting both patients' and researchers' interests only 19% of the time. Therefore according to this research, from an individual point of view, the most rational behaviour is not to trust the researcher and not to enrol in a clinical trial. Nonetheless, the authors acknowledged that in this instance they employed a 'relatively narrow' view of the trust-risk model which did not incorporate broader societal dimensions of trust including virtue goodwill or moral integrity.

It would require a mathematician to fully critique this model but on face value it demonstrates the inadequacy of a purely rational-choice model, and its assumption that all individuals, if provided with accurate information, will make a rational decision in their own best interests (Lidz, 2006; Corrigan, 2003; Alderson & Goodey, 1998). Consequently, a view of consent, premised on a 'real' standard or ideal, which can be achieved through the adequate exchange of 'medico legal' information alone has been criticised as too simplistic (Alderson & Goodey, 1998) and as 'empty ethics' for stripping consent of its social, cultural, political and clinical context (Corrigan et al, 2004;2009). Furthermore questions have arisen around how autonomy has been operationalized as informed consent (Corrigan et al., 2009; Manson & O' Neill, 2007; Alderson & Goodhey, 1998; Gillon, 1994) as it fails to acknowledge the relational and ongoing nature of autonomy (Kukla, 2005). Translating the concept of autonomy into an individual's ability to engage in practical reasoning in order to make an autonomous decision does not take account of the rich social context in which people's life narratives exist (Kukla, 2005). Moreover, Kukla (2005) suggests that reducing autonomy to informed consent fails to take into account of the wider social context in which healthcare relationships

and a patients' autonomy exists. Furthermore, focusing on a patient's decision made in response to a discrete choice may function instead to absolve clinicians (and researchers) of certain kinds of responsibility, rather than supporting a patient's on-going autonomy (Kukla, 2005).

Upholding autonomy is further complicated in individuals who are unable to provide informed consent, including young children or adults who lack capacity. Obtaining the assent of a child and the permission of a parent or guardian is not the same process as obtaining informed consent from a competent adult (Nuffield Council on Bioethics, 2015; Committee on Bioethics, 1995). When parents are asked to consider entering a young child in a trial, they are exercising responsibility on behalf of their child and are not directly exposed to the consequence of the trial outcome. Parents and trial practitioners face a new set of issues when children are considered old enough to have an opinion and be involved in decision-making (Broome & Richards, 2003; Olechnowicz et al., 2002). These differences have lead to the perception that recruiting children to clinical research is 'more complex' compared to the adult context (Shilling & Young, 2009; Caldwell et al., 2003; 2004), arising from a child's changeable development status and level of independence (Alderson & Morrow, 2011; Manson & O'Neill, 2007; Alderson, 2007).

Despite conceptual differences in the recruitment process involving children and adults, (where a child's parent or guardian must provide permission in addition to the child's assent if s/he has the maturity to do so) (Caldwell, 2003; 2004; Punch, 2002) this scoping review identified a paucity of research examining how these differences may inform understanding of the phenomenon of trial recruitment. Only one study, in the context of informed consent for oncology trials, has directly compared the views of parents of child patients with those of adult patients (Simon

et al., 2004). Adult patients were found to be more fully informed than parents, which Simon et al. (2004) attributed to the additional complexity of the family context. Simon and colleagues viewed this added complexity as factors relating to the parental role of proxy decision-making in which they either make a decision on behalf of their child or negotiate their child's involvement in the decision-making process. However, this study did not access the perspectives of children or practitioners and was primarily focused on researcher defined concepts of understanding, rather than the priorities of those involved. Consequently, an in-depth account of the psycho-social influences on how individuals viewed trial recruitment was unclear.

1.5 Altruism: cause for celebration or concern?

Altruism too has become a prominent theoretical construct in this field. It refers to a patients' personal motivation to contribute to the greater good by putting themselves out for the benefit of future patients (McCann et al., 2010; Balfour et al., 2010; Simon et al. 2006; Garcea et al., 2005). While altruistic motives for participation in trials have been identified in both adults and children, other motives such as personal benefits have also been identified, and it is not always clear how the two interrelate (Edwards et al., 1998). Furthermore, there is inconsistency in how altruism is constructed by patients, parents and researchers. Altruism may encompass: a desire to contribute to scientific knowledge; future benefits for other patients with the same condition and patients in a more general sense; the ethic of reciprocity to past patients and the investigator; and the social value of participating in research (Simon et al., 2006; Garcea et al., 2005). However, in much of the trial recruitment research altruism is measured by participants rating the importance of statements such as 'I wanted to help future patients or 'I wanted to help advance

medical treatments' (Tait et al., 2003; Henzlova et al., 1994). This structured methodology provides limited insights into patients' underlying motives. Moreover, it remains unclear to what extent altruism is invoked by the self-presentational factors and indeed by practitioners during the consent process (Spriggs, 2006).

Researchers have suggested that the separation of potential benefits to self from the motive to help future patients with the same condition, as typified by statements such as *We cannot promise the study will help you but the information we get from this study will help improve the treatment of people with* [name of condition] which is found in most trial documentation, invokes an expectation of altruism (Simon et al., 2006). Nevertheless, the role and significance of altruistic discourse during recruitment encounters are debated (Rennie, 2011; Williams et al., 2008; Ladd & Forman, 2006). Proponents argue that discussions of altruism are an essential part of the trial consultation, helping to dispel the therapeutic misconception and to ensure the research goals are clear (Joffe, 2006). Indeed a personal motivation to take part in a trial has been viewed as involving a degree of altruism if consent is considered to be rational, as the primary aim of a trial by its very nature is to contribute to generalisable medical knowledge, rather than to benefit individual participants (Hester & Hackler, 2006; Edwards et al., 1998; 1999).

In contrast, Horrobin (2003) suggests that invoking altruistic considerations for trial participation during the consent process is disingenuous and misrepresents the nature of research, as clinical trials serve the interests of various parties, including commercial sponsors; and the primary motivator for patients is their well being, with the greater good being secondary. Nevertheless, empirical evidence has consistently indicated that participants, both adults, children, parents of child

participants and practitioners commonly view altruistic considerations as an important component of the recruitment process.

Altruism refers to an individual's desire to help others at a personal cost and without rewards (Batson, 2014; Scott & Seglow, 2008). Nevertheless, psychologists and biologists, in particular, have critiqued this singular notion of altruism as representing an unattainable ideal that is incompatible with evidence that human behaviour is rooted in self-interest (Dawkins, 2016; Silk, 2013; Scott & Seglow, 2008). In order to accommodate this disparity between the selfless act of helping others and self-interest, biologists have proposed various theories, including the idea 'reciprocal altruism' (Silk, 2013), a form of kindness that results in mutual benefit with the belief that it might be beneficial to incur costs, if there is a chance of the altruistic act be reciprocated (Trivers, 1971).

The 'golden rule' present in many religious and ethical traditions 'do unto others as you would have them do unto you' (Scott & Seglow, 2008), is not dissimilar to the notion of reciprocal altruism (Trivers, 1971) and in turn is not dissimilar to the notion of the 'gift relationship', represented by the archetypal altruistic act of blood donation (Evans & Ferguson, 2014; Scott & Seglow, 2007; Titmuss, 1970). However, the literature on blood donation has conceptualised altruism as multifaceted, reflecting a number of related processes as opposed to a singular construct (Evans & Ferguson, 2014).

Whether trial participation can be viewed within the same theoretical or ethical framework as blood donation is unclear and the role that altruistic motivation plays in the recruitment and decision-making processes for clinical trials continues to be debated (Jansen, 2009; Williams et al., 2008). While typically not positioned as a

primary motivator, empirical evidence indicate that altruism is an important motivating force for many trial participants and blood donors (Evans & Ferguson, 2014; Truong, 2011; Simon et al., 2006). Ideas of kinship have been found to motivate blood donation, for example, the belief that 'If I gave blood there is more chance of close relatives receiving it if they need it' (Evans & Ferguson, 2014). Similarly, the ideal of reciprocity or paying back those that previously participated in research has been found to motivate trial participation (McCann et al., 2010; Lowton, 2009).

However, in paediatric oncology trials, findings show that altruistic discourses initiated by practitioners did not influence whether parents enrolled their child in the trial or the reasons they gave for doing so. In addition, Wasson (2006) poses an important question arising from Simon's (2006) finding - 'do people weigh altruistic consideration differently for themselves versus others'. Spriggs (2006) proposes that altruism is not something that another person can volunteer on somebody else's behalf. If this is the case, references to altruistic motives cannot be taken at face value. It is unclear from Simon et al.'s (2006) findings how parents conceptualise their altruistic motives in relation to their children.

In-depth qualitative approaches have distinguished 'weak' altruism and 'conditional altruism' (McCann et al., 2010; Canvin & Jacoby, 2006), with the former characterising a participants' desire to maintain self-interest while also expressing a desire to help (Canvin & Jacoby, 2006). 'Conditional altruism' characterises a similar idea in that while an altruistic tendency may encourage trial participation, this motivation is still 'conditional on perceiving a personal benefit and an absence of overriding concerns' (McCann et al., 2010).

Nevertheless, debates continue about what constitutes altruism, and about conceptual differences between 'altruism-by-proxy' among parents compared to direct altruism among adult patients. Furthermore, most empirical evidence lies in the field of oncology (Truong et al 2011; Wendler & Jenkins, 2008; Joffe, 2006) and further research is needed to examine the role and conceptualisation of altruism in paediatric and adult settings beyond oncology, which includes the perspectives of both the parent and child.

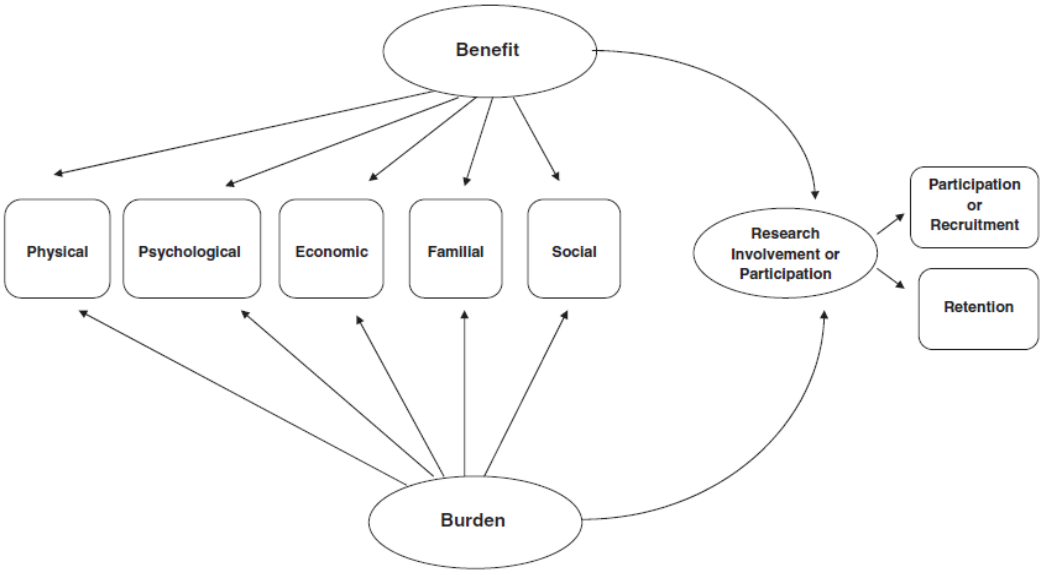
1.6 Developing a model of trial recruitment

Relative to the volume and diversity of the empirical evidence on recruitment, the corresponding literature aimed at developing a theory or conceptual model of recruitment is small, with much of this literature published more recently. Within this section, I will examine models which have drawn exclusively from empirical data and those which used established theory e.g. Health Belief Model, (Janz & Becker, 1984); Social exchange theory (Homans, 1961)

1.6.1 A personal balance account

Most models focus solely on one side of the recruitment exchange -the process of decision-making, as viewed by a potential participant (e.g. McCann et al., 2013 Ulrich et al., 2012; Lowton, 2005 Mueller; 2004; Verheggen et al., 1998). These models are based on accounts of patients describing factors which influenced their chosen course of action when approached to take part in a clinical trial, and attempt to explain how potential participants negotiate trial participation decisions. A recent example is based on 32 qualitative interviews with adults enrolled in an oncology trial. This model incorporates five key dimensions of the potential benefits and burdens a patient may navigate before coming to a decision (*Figure 1.1).* These dimensions include health related or physical aspects, psychological aspects; familial and support components, economic concerns and societal factors, all of which have the potential to influence an individual's decision to participate in a clinical trial.

FIGURE 1.1: Ulrich et al.'s (2012) model of the benefits and burdens of research participation



Parallels can be drawn between this model and an earlier proposal by King (2000), who described the need to differentiate between the types of benefits that participants viewed as arising from participation in clinical trials. King (2000) suggested that the benefits for potential participants may comprise; direct clinical benefits from the intervention itself, indirect benefits from being a participant in a trial, such as increased monitoring or personal health information, and what King(2000) refers to as 'aspirational benefits' i.e. potential future benefits to society and future patients. King's (2000) 'aspirational benefits' appear synonymous with 'psychological' motivators described by Ulrich et al., (2012) and the broader altruistic discourse in the recruitment literature (e.g. Simon et al., 2006). However, Ulrich et al.'s (2012) model captures both burden and benefit across each dimension, in contrast to King's (2000) account which solely focuses on differentiating dimensions of benefit. A further strength of this model is that it extends beyond an

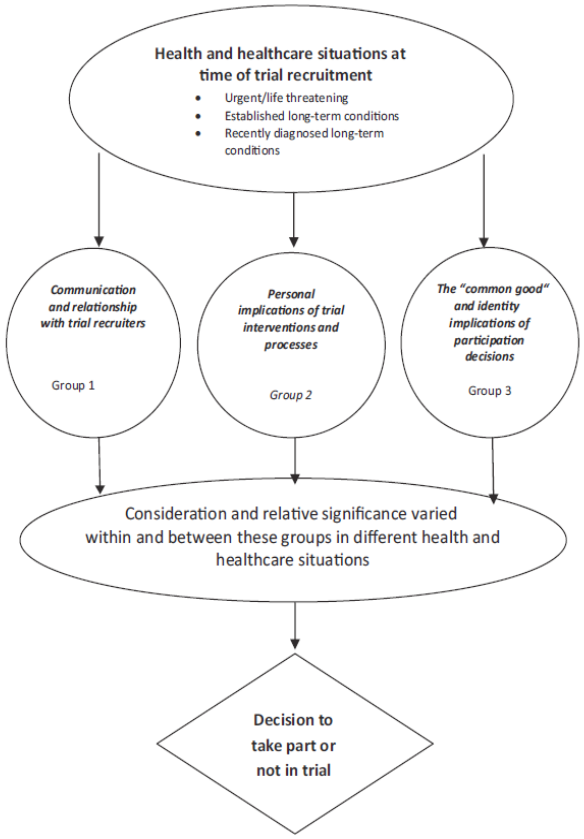
individual's practical reasoning of medico-legal trial information to include broader psycho-social, familial, economic features of the decision-making process. However, this model does not provide insight into how individuals weigh the benefits and burdens of research participation, or the diverse way participants approached their decision to participate. How these dimensions may interrelate or what factors may mediate personal judgement of these dimensions requires further evaluation (Ulrich et al., 2012).

Based on a meta-synthesis of 12 qualitative studies, across a range of different health contexts (including accounts of patients and parents of child patients) McCann et al. (2013) developed a model which provides valuable insights into how potential participants' health status at the time of recruitment can mediate 'decision influencing judgements' *(Figure 1.2)*.

These decision influencing judgements include:

i) informants' communication and relationships with recruiters
ii) personal implications of trial interventions and processes;
iii) the 'common good' and the implications of participation decisions for the identity of informants.

FIGURE 1.2: McCann et al's (2013) conceptual model of factors influencing trial participation



In contrast to models derived from the data Verheggen et al. (1998) used an extended form of the Health Belief model to develop an explanatory model based on statistical analysis, to understand how patients weigh the benefits and burdens of trial participation. The HBM was originally developed in the 1950s to understand people's poor uptake of disease prevention initiatives but has since been developed and applied to a range of health context behaviours (Janz & Becker, 1884). Verheggen et al. (1998) extended the HBM to include a number of general health values and an instrument of health related locus of control detailed in *Figure 1.3*

which incorporates a kind of cost benefit analysis to predict health related behaviour.

FIGURE 1.3: Verheggen's (1998) model of explanation for trial participation

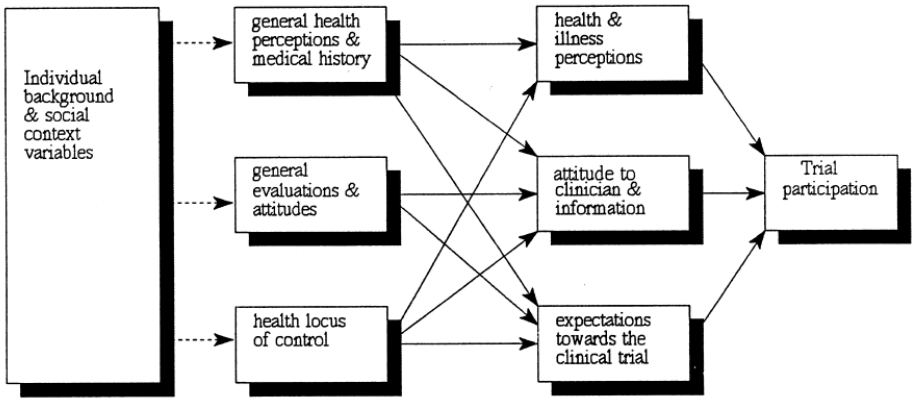


Fig. 1. Model of explanation for trial participation.

From this position trial participation was viewed as 'illness coping behaviour'. The model of explanation detailed in Figure 1.3 was used to form the theoretical basis for a survey designed to gain insight into the psycho-social determinants of patients' trial participation decisions. Based on data obtained from 198 adult patients who had been approached to participate in one of 26 clinical trials across a diverse range of clinical contexts this model proposed a 'personal balance account' in which potential participants are viewed as weighing up the physical and emotional value they hope to gain through trial participation, against the expected risks and burdens associated with the trial.

A strength of this model is its ability to capture how the factors influencing patients' decision to participate in a trial are diverse and interactional. In addition, the model

identifies important mediating factors including the significance of recent medical experiences and the nature of an individual's illness.

However, not all the determinants of the model were shown to be significant and consequently not all the variance was accounted for. For instance, the model showed how information disclosure did not appear to be a determinant in explaining trial participation and evaluations of 'medico-legal' requirements of informed consent were not considered as reasons to participate or not. These findings highlight the strength of models which are grounded in data (Strauss & Corbin, 1998) and the limitation of models solely informed by existing theory, where relevant factors may be overlooked.

Nevertheless, these decision-making models appear to implicitly and explicitly draw upon elements of rational choice theory to explain how trial participation decisions may be negotiated. However, models guided by normative models of decision-making assume people are 'rational' and deliberative in how they approach decisions, and therefore may overlook more intuitive relational processes.

1.6.2 Negotiating risk and uncertainty

The issue of managing risk and uncertainty has featured prominently in other theoretically informed accounts of why people agree to take part in clinical research, particularly in the context of chronic health conditions including HIV and CF (Yang et al., 2010; Lowton, 2005; Mueller, 2004). Mueller (2004) developed Strauss et al.'s (1985) work on contingency to explain how individuals made sense of their decisions to participate in a 'HIV/AIDS' clinical trial. Strauss et al. (1985) conceptualised contingency as the unexpected or difficult to control features of

health care work that patients and practitioners attempt to manage. Mueller (2004) applied this concept to characterise the work or effort a patient engages in to control or manage uncertainty by declining or consenting to clinical trials. Qualitative data from 24 participants in an HIV/AIDs trial showed how individuals interpret and act on the uncertainties intrinsic to clinical research based on negotiations involving clinical, social and technical contingencies. Clinical contingencies related to an individual's perception of their health status at the time of the approach and the perceived influence of trial participation on their health. For individuals with uncertain health, trial participation appeared to act as a way of dealing with this uncertainty and offering hope. Social contingencies included perceptions of trust, self-interest, and altruism; while technical contingencies referred to the value assigned to trial procedures and protocol design, such as design flexibility and level of monitoring. Although Mueller (2004) developed this framework in the context of HIV/AIDs, she believed it might have wider applicability in offering a conceptual framework to bring together disparate literature on patient recruitment to clinical research.

Each of these contingencies was useful in highlighting key features of the decision-making process from the patients' perspective. However, this framework did not consider the perspective of the recruiter and only included patients who had consented to a trial. Mueller (2004) herself also acknowledged that further research was needed to gain insight into factors which may influence the prominence of certain contingencies and how clinical, social and technical contingencies are negotiated between researchers and patients.

Lowton (2005) also drew on sociological theories of risk to interpret qualitative data obtained from 31 adult patients with CF. Bloor's systems of relevance framework for

risk behaviour and risk reduction was used to inform how individuals negotiated their course of action when approached to take part in clinical research. Consistent with Dixon-Wood & Tarrant's (2009) work, Lowton's (2005) study included patients who had been approached to take part in all types of medical research, including clinical studies and clinical trials. This design enabled patients' perception of risk associated with different research designs to be examined.

Bloor's (1995) sets of conceptual oppositions: habituation and calculation, constraint and volition were applied to the dataset to represent a range along a continuum of risk behaviour rather than absolute distinctions. According to this conceptual framework, Lowton (2005) described participants' calculations about risk behaviour as a conscious deliberation of the costs and benefits of individual actions. Lowton (2005) defined the notion of risk and constraint as referring to both social and health constraints such as age, perception of health and obligations to family or employers. Patients' perceptions of current and anticipated future health states informed their assessments of the 'necessity' of their research participation. For example, one patient perceived that if she were really ill, she would 'try anything' and others whose health could not be maintained actively sought participation in clinical trials. Older patients and patients who viewed their health as controllable were 'more careful' about decisions to participate, and they were, therefore, less likely to participate in RCTs perceiving them as posing more risk than observational studies involving the giving of blood samples. Lowton (2005) also proposed that patients may become habituated or accustomed to being involved in research, to the point where they enrolled in research without seeming to weigh up the costs and benefits. The two main factors that were influential in adults' decisions to habitually accept research participation requests were the type of research project and trust in the specialist centre and practitioners.

These findings showed that personal motivations were broadly similar in this as in other health contexts (e.g. Madsen et al., 2007; Fry & Dwyer, 2001). Nevertheless, these findings prioritised patients' perspectives; clinicians' perspectives were not included. In addition, the patient sample was drawn from one CF centre, so it is unclear whether these findings are applicable to the wider CF community or whether they could be extended to research experiences within paediatric CF settings.

1.6.3 Recruitment as a social act

In contrast to models discussed up to now, which have foregrounded individualised decision-making; several authors have positioned trial recruitment within a broader social context (McGregor et al., 2010; Dixon Woods & Tarrant, 2009; Morris & Balmer, 2006). While these authors still base their accounts of recruitment on data obtained from potential participants, they emphasise the social exchange dimension of recruitment. McGregor et al. (2010) used the principles of social exchange theory (SET) to conceptualise the process of trial recruitment and retention. Social exchange processes have been found in every documented human culture (Cosmides et al., 2010; Isacc, 1978). Theories that explain these processes have also been influential across disciplines such as anthropology, social psychology and sociology, which are united by the underlying assumption that social exchange involves a series of interactions that generate obligations (Copranzano & Mitchell, 2005; Emerson, 1976).

From this position, McGregor et al. (2010) viewed recruitment and retention as being dependent on the formation and maintenance of relationships. According to the principles of SET, these relationships develop as a result of a mutual exchange of resources, which can be symbolic or material, in which each individual believes that

each party within the relationship will benefit (Homans, 1958). Participants will therefore only be recruited and retained in a trial if doing so involved a mutually rewarding exchange, leading to a long-term mutually beneficial relationship (McGregor et al., 2010).

From a SET perspective, the quality of the relationships is emphasised, and successful recruitment is viewed as being dependent on a subjective cost-benefit analysis by each involved party. For relationships to be established and maintained, benefits must outweigh perceived costs for both patient and researcher. Furthermore, SET acknowledge the power dynamics of relationships during the research process (McGregor et al., 2010) arising from the dependence of one individual upon another, with a power dependence assumed to be most apparent at the time of recruitment, when the patient may be more vulnerable to exploitation. Furthermore, trust is also essential to the establishment and maintenance of exchange relationships, however, the exact mechanism as to how trust informs the recruitment process remains unclear (Townsend et al., 2008; Lawler, 2001).

While McGregor provides a convincing argument about the relevance of SET in theorising recruitment practice, this theoretical account was based on one particular trial, the nature of which may have led to an emphasis on the significance of research relationships. This trial evaluated a relatively low risk post-surgical device to aid recovery from sternotomy in older patients (Women's Recovery from Sternotomy Trial, WREST). It is conceivable that the elderly retired individuals within this trial may have viewed the prospect of regular positive interactions during a period of post surgical recovery as a primary benefit and a significant motivator in their decision to participate. In contrast for a young adult with a family

and employment commitments, regular interactions with a researcher may not be perceived as carrying the same benefits.

In contrast to a focus on the immediate social relationship between researcher and participant, Dixon-Wood & Tarrant (2009) proposed a broader theoretical explanation of trial recruitment informed by societal level theories of cooperation and social organisation. Based on qualitative evidence of participants' experiences and views of being invited to take part in one of three different clinical research studies, Dixon-Wood & Tarrant (2009) argue that participation in research is a 'collaboratively oriented action'. In this model, cooperation provides a way of thinking about how people come to engage with clinical research that stands in contrast to individualist models concerned with cost-benefit analysis and the adequacy of consent. While the evidence mirrored other studies in the diversity of personal motives, participants' accounts were unified by a perception that individuals would be contributing to the 'public good', which Dixon-Wood & Tarrant (2009) suggest can be understood as an example of what Olson (1965) terms 'collective action'.

This framework for understanding trial participation decisions illustrates the significance of the social structure of research in influencing how individuals made sense of their participation decision. According to this account personal judgements and actions were institutionally and organisationally structured. Participants' decisions assumed the existence of regulatory and institutional safeguards and trustworthiness. Consequently, the symbolism and rituals enacted by qualified professionals were more influential in participants' accounts than the detail or content of various communications.

A strength of this theoretical explanation of trial recruitment was that it was informed by a large, diverse evidence base, including 128 participants, which integrated children, parents, pregnant women and adults' accounts. Furthermore, unlike other studies, which have focused primarily on clinical trials, this framework of cooperation was based on evidence from three different clinical studies with varying cost-benefit ratios. These included: a paediatric study involving surplus cancer tissue banking, an RCT of emergency treatment for women experiencing pre-term labour and a genetic epidemiology study of blood pressure regulation involving healthy volunteers. However, this theoretical framework is only informed by empirical examination of one side of the 'cooperative bargain', that of the participant.

Further research including evidence from both sides of the exchange has the potential to examine processes of cooperation and collective action further. Another potential limitation is that this theoretical account was informed by evidence from people who consented to participate in these studies and it is unclear how evidence from decliners would be reconciled with this model of cooperation. Consequently, a central facet of Olson's (1965) logic of 'collective action' has not been addressed - that where individuals believe they can receive the benefits of cooperation without contributing, they may be inclined to 'free ride' leaving cooperation to others (Olson, 1965). The extent to which an individual who shares a common interest will bear the costs of the public good could be informed by exploring the views of decliners across varying cost-benefits.

Further along, this continuum of cooperation is a potentially more controversial view of clinical research participation, in which participation is viewed as a moral duty or obligation and the morality of the 'free-rider' is brought into question

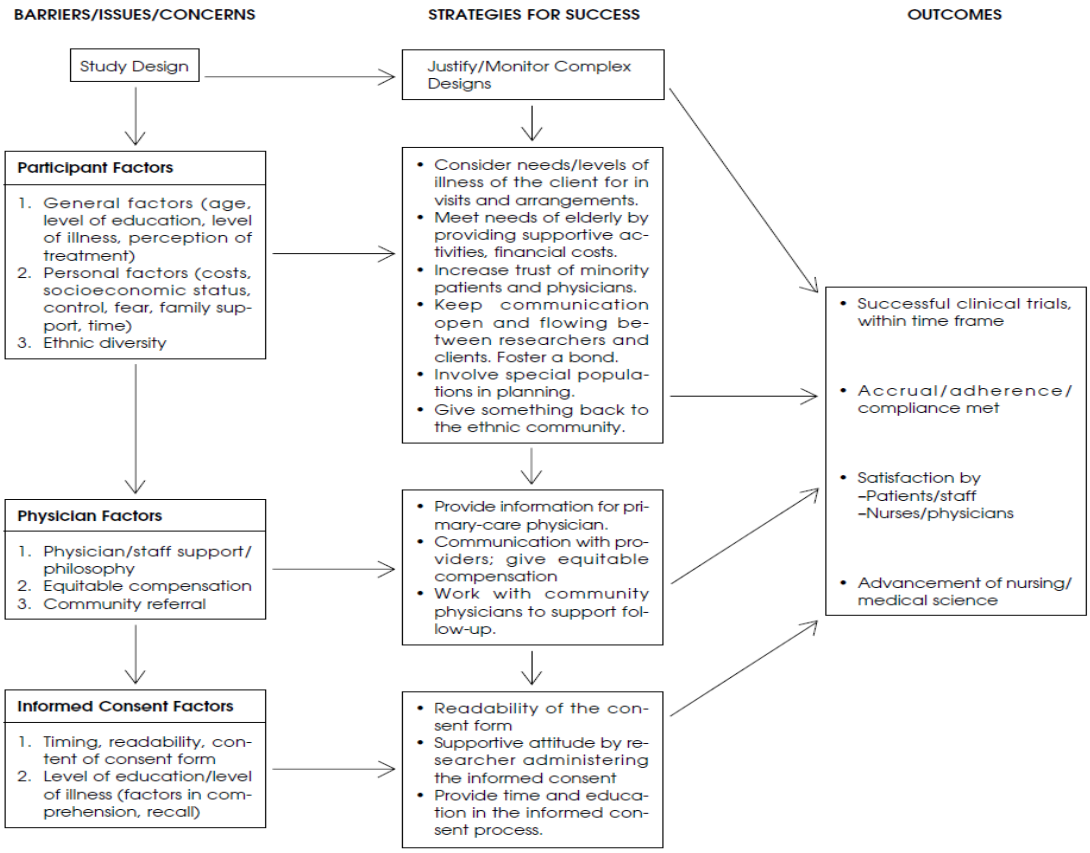
(Schaefer et al., 2009; Harris, 2005; Caplan, 1984). Consistent with Dixon-Wood & Tarrant's (2001) view, this position is also derived from the perspective that scientific knowledge derived from clinical research is a 'public good' in which all people stand to benefit. Therefore, support and participation in clinical research is viewed as a social duty or responsibility. Rather than the current social norm that people participate only if they have good reason, the public good position implies that people should participate unless they have good reason not to (Schaefer et al., 2009).

Underpinning this perspective is the idea that there is an obligation to share the responsibility of research participation because the benefits of research are available to all. This position is clearly subjugated by the dominant view of respect for an individual's autonomous choices and the robust discourse on protection of human subjects. Nevertheless, it raises important questions about the potential ramifications of recasting research participations in this way (Rennie, 2011).

Conceptual models identified in the literature which drew on empirical evidence from both sides of the recruitment exchange, that is those being recruited and those doing the recruiting, were limited (Lengacher et al., 2001; Hughes-Morley et al., 2015).

Lengacher et al.'s (2001) work summarised empirical evidence in the literature on barriers to recruitment and corresponding strategies to overcome these to illustrate a model of successful trial recruitment and retention. Study design, participant factors, physician factors and the informed consent process were identified as key features which had the potential to influence trial recruitment and retention *(Figure 1.4).*

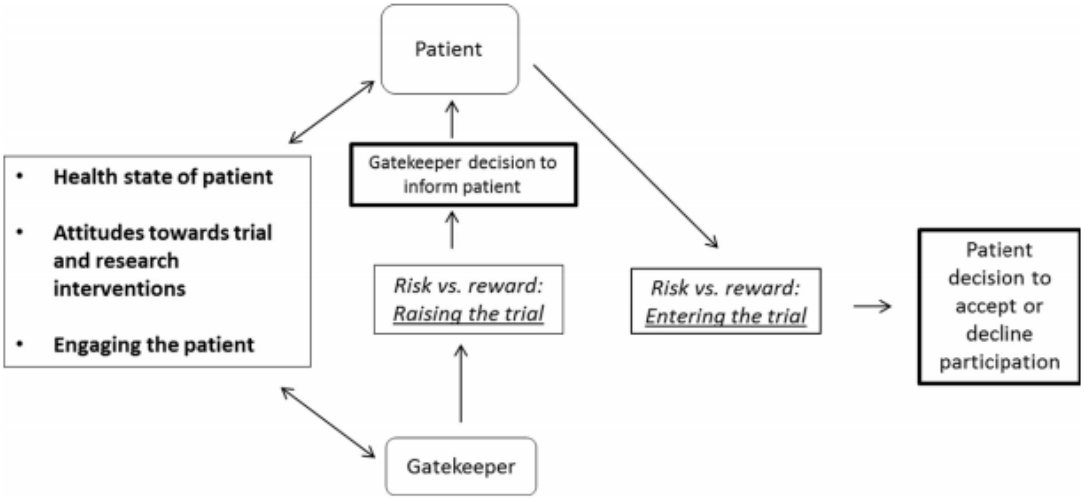
FIGURE 1.4: Lengacher's (2001) model for clinical trial participation



While this model is useful in summarising findings within the literature, it does not provide any theoretical insights into how these factors can be unified conceptually. A more comprehensive conceptual model derived from data obtained from both recruiters and participants' accounts of recruitment is presented by Hughes-Morely et al. (2015) *(Figure 1.5)*. Based on a systematic review and meta-synthesis of published qualitative studies examining recruitment into depression trials, Hughes-Morely et al. (2015) proposed an initial explanatory model to summarise factors influencing the recruitment process *(Figure 1.5)*. An important aspect of this model is that it identifies an additional key point in the recruitment process, the

gatekeeper's decision about whether or not to inform the patient about the opportunity to participate in a clinical trial. The model, therefore, captures the 'weighing up' process from both sides of the recruitment process. In addition, this model also identifies significant mediators of the process which includes: health context, attitudes towards trials and research interventions and issues around engagement.

FIGURE 1.5: Conceptual framework of factors influencing the decision to participate



Even though this model has been developed from evidence drawn from the distinct clinical context of depression, it is conceivable that this framework would have wider applicability, as the aspects identified are consistent with those of other models and findings within the broader empirical recruitment literature. Nevertheless, the authors themselves acknowledge that this framework represents

an 'early effort to develop and explanatory model' and that further qualitative research is required to gain further understanding into the weighing up process.

1.7 Summary and positioning my case

This scoping review has confirmed that clinical trials are viewed as indispensable for evidence-based medicine, yet recruitment remains challenging and the processes involved are inadequately understood. Distinct discourses on clinical trial recruitment have emerged, yet there is a paucity of conceptual frameworks that can unite this disparate literature from both sides of the recruitment exchange. The dominant discourses have centred on improving accrual of participant numbers or the ethical conduct of recruitment. While these discourses are important, they do not constitute theories of recruitment that can inform the development of optimal recruitment practices and future recruitment research. Neither are they able to explain the reported difficulties with recruitment, such as why certain trials recruit more effectively than others (Dawson, 2009; Campbell, 2007). Those difficulties can be profound, for example, evidence indicates that many 'perhaps even most' competent adults do not achieve a level of understanding to the degree necessary to uphold the ideal of 'fully informed consent, indicating that this ideal is largely unattainable (Dawson, 2009).

Qualitative research which has focused on understanding and examining the range and complexity of perceptions held by individuals who have had direct experience of recruitment is providing a more unified in-depth understanding of the process. Instead of emphasising generalisability across individuals, groups or settings, qualitative research is able to generate rich theoretical concepts enabling the development of theoretical models and frameworks (Murphy et al., 1998).

Consequently, qualitative evidence has led to the development of important insights into how people make sense of research invitations within the context of their personal illness trajectory and life circumstances. These insights extend beyond a primary concern with the adequacy of informed consent and information exchange. However following this scoping review several gaps within this literature were identified which this study aims to address.

1.7.1 Paucity in qualitative studies with a comparative focus

Despite comparative qualitative research being recognised as an important analytical tool for providing theoretical insights into complex social phenomenon (Bradley et al., 2007; Stake, 2003; Mason, 2002) there is a distinct lack of qualitative research which directly compares recruitment experiences across settings. In particular, there are important conceptual differences in the recruitment process across adult and child settings (Truong et al., 2011; Simon et al., 2004; Caldwell 2003; 2004; Punch, 2002). The distinct social and legal differences with regard to the position of children, adults and parents in society have the potential to serve as important comparative foci within qualitative recruitment research.

Despite the changing view of childhood in society, Goldstein's (1977) quote below captures a conventional pervasive view of the potential divergence between the role of child, adult and parent in society

> *To be a child is to be at risk, dependent, and without capacity or authority to decide what is "best" for oneself.*
>
> *To be an adult is to be a risk taker, independent, and with capacity and authority to decide and to do what is "best" for oneself.*

To be an adult who is a parent is to be presumed in law to have the capacity, authority, and responsibility to determine and to do what is good for one's children.'

It is likely that trial recruitment in the paediatric settings is more complex compared to trials involving autonomous adults (Caldwell, 2004); therefore, it is anticipated that a comparative focus across adult and child settings in the context of cystic fibrosis will fill an important gap in the recruitment literature, providing an analytical tool to understand further the nature of recruitment and the psycho-social context in which it occurs.

1.7.2 An underrepresented population

Much of the evidence base is in the field of oncology, leaving many underrepresented populations. Evidence on trial recruitment processes in CF is minimal, with no comparative work across adult and child settings despite it having proved to be an ideal opportunity to investigate how invitations to participate in clinical research are experienced within a defined patient group (Dobson et al., 2015; Lowton, 2005).

CF is the UK's most common autosomal recessive disease, which is now typically diagnosed at birth. Due to advancements in treatment, children born in the 2000s are now predicted to reach the fourth or fifth decade of life (Dodge et al., 2007) and CF care has changed from being mainly a paediatric speciality to both a child and adult specialty (Thomson & Harris, 2008; Robinson & Robertson, 2003). Clinical trials are critical for assessing the effectiveness of therapies for CF, and consequently, adults and children with long-term conditions such as CF are an intensely researched population - making this an ideal context to investigate trial

recruitment (Dobson et al., 2015; Briggs et al., 2006; Lowton, 2005). Moreover, it is a promising time for the CF community, as over the past ten years basic science research has resulted in some potential new therapies for CF. However; it is also a challenging time with a large number of international multicentre trials attempting to recruit patients. Patients and their families will be faced with a bewildering range of clinical trials offering new therapies, including those funded by pharmaceutical companies, and often involving complex or early phase designs. These treatment advancements depend on adequate recruitment to clinical trials, which remains a significant challenge (Cheng et al., 2000; Briggs et al., 2006). Furthermore, despite the widespread involvement of children in CF trials, this review did not identify any qualitative research comparing recruitment experiences across adult and paediatric settings within the context of CF, making this a significant gap in the recruitment literature.

1.7.3 A paucity of literature incorporating recruitment from both sides of the exchange

While some conceptual models do exist with more recent models informed by qualitative evidence, most of these have focused on the decision-making process of the potential participants rather than aiming to understand recruitment as a process, including individuals from both sides of the exchange. Qualitative research examining recruitment from both sides of the exchange is less prevalent, and there is no qualitative work of this nature comparing across adult and child settings. Examining recruitment from 'multiple' perspectives is providing a greater understanding of the complexity and interrelation of factors involved (Campbell et al., 2007). Furthermore 'multi-perspective' qualitative interviewing is a critical methodology for understanding the needs, beliefs and experiences of those receiving and providing health care (Kendall et al., 2010).

To address these key gaps identified in the literature, this study will explore experiences of trial recruitment from the perspective of:

- adult patients with CF
- children with CF
- parents of children with CF
- practitioners involved in recruiting children or adults with CF to clinical trials

This thesis aims to contribute to the trial recruitment literature both conceptually and empirically through a comparative exploration of experiences of recruitment in the context of CF across adult and paediatric settings. It also aims to contribute to uniting recruitment evidence conceptually, empirically and pragmatically while ensuring the focus is continually informed by those directly involved.

CHAPTER 2: METHODOLOGICAL CONSIDERATIONS

2.0 Introduction

How researchers proceed with any project depends on their assumptions including; their beliefs about the nature of reality (ontology), the nature of knowledge and how it can be acquired (epistemology) and the purpose and goals of the research (Silverman, 2013; Travers, 2001). There is a general agreement that understanding and acknowledging the philosophical and theoretical backgrounds associated with different approaches to social science research will contribute to better practice and provide ways of assessing the integrity and authenticity of research (Ritchie et al., 2014). A researcher must find the best orientation for achieving the aims of the research through a detailed examination of the purpose and context of the study, combined with an examination of the researcher's own personal orientation (Merriam, 2009).

The case study conducted in this thesis was primarily exploratory aimed at increasing understanding about the phenomenon of recruitment from the perspectives of those with firsthand experience of the process. A qualitative case study in a stable underrepresented population enabled a detailed, in-depth study or investigation into the nature and complexity of the phenomenon of trial recruitment. In this chapter, I will provide a rationale for adopting this methodology. I will examine key epistemologies and theoretical perspectives which have influenced this case study. Finally, I will orientate my study in relation to these epistemologies and discuss how this methodology was adopted.

2. 1 Case study and theoretical influences

The case study has a long and varied history and is associated with several disciplines including history, anthropology, sociology, education, medicine and psychology (Thomas, 2011; Platt, 2007 Hamel et al., 1993). It should also be noted that the term 'case study' can be used in a variety of ways and not all of them are clear. For instance, the term can be confused with casework in social services, case studies in teaching and case report in medicine (Merriam, 2009; Platt, 2007; Hamel et al., 1993). Among social scientists, a case study has a range of interpretations, and it remains unclear whether the case study constitutes a methodological choice, a design strategy or an approach to the study of single entities (Baxter & Jack, 2008; Platt, 2007; Hamel et al., 1993). Descriptions of case study include: the study of an issue explored through one or more instances within a bounded system such as a particular setting (Cresswell, 2007) 'an empirical inquiry that investigates a contemporary phenomenon within its real life context' (Yin, 2009) and an in-depth investigation and analysis of a single or collective case, intended to capture the 'particularity and complexity' of the object of study (Stake, 1995).

Different advocates of case study appear to emphasise particular ways of defining the 'case' with the use of varying terminology. Debates exists about whether the case should be defined at the outset or emerge as the inquiry progress (Thomas, 2011a; 2011b). Suggestions of how to define a case may include time, place, context, activity or situation (Yin, 2009; Stake, 2003; Creswell; 2003; Miles & Huberman, 1994). Thomas (2011a) defines the 'thing' to be explained as the 'object' of the study and the 'thing' doing the explaining as the 'subject' of the case study, and a case must be 'of' something. Regardless of definitional problems, most accounts view case study as a detailed, in-depth study or investigation of singular phenomenon

which can be an event, situation or experience and may involve the use of diverse methods of data collection and analysis (Simmons, 2009; Willig, 2008). Indeed much social science research could be conceived as a form of case study because it usually involves the analysis of social phenomena specific to time and place (Ragin, 1992).

Unlike other approaches, case study does not emerge from a particular social scientific tradition - for example, ethnography has its roots in anthropology with a special focus on culture. Varying approaches to case studies place emphasis on different features of the methodology, whether it is exploratory, explanatory, descriptive, empirical, or evaluative (Thomas, 2011a). Furthermore case studies are neither new nor essentially qualitative and may include quantitative as well as qualitative data (Hyett et al., 2014). Ultimately the way a case is defined is dictated by what the researcher aims to achieve or wants to know. However different ideas about what constitutes a case study methodology to some extent reflect the diversity of epistemological starting points of researchers who use this approach (Thomas, 2011b).

Many researchers using case study have mostly situated their work within either a largely post-positivist paradigm or constructionist or interpretive paradigm (Hyett et al., 2014; Thomas 2011b; Brown, 2008). Some authors have positioned case studies somewhat outside particular paradigms, as a flexible, pragmatic approach or 'bridge across paradigms' (Luck et al., 2006). However, many inconsistencies exist with regards to interpretations of epistemological and theoretical perspectives, and how these terms are used and defined within the literature (Seale et al., 2004; Patton, 2002). Therefore I considered it necessary to make explicit my understanding and interpretation of these positions to ensure integrity and coherence in my methodological considerations underpinning this study.

2.1.1 Defining positivism and post-positivism

To fully comprehend the position of positivism and post-positivism it helped to briefly trace the evolution of this term and its relationship to ideas about objectivity and scientific realism. Crotty (1998) uses the term 'objectivism' to describe what other authors have termed objectivity or scientific realism (Smith, 1998; Hacking, 1983), in which truth is believed to reside in the object of analysis and can be known through systematic study (Crotty, 1998). A belief in an objective account of reality forms the foundation of western science and has strongly influenced the field of the natural or physical sciences. Scientific inquiry is perceived as progressing towards universal truths about nature (Smith, 1998). The world described by objective scientific inquiry adopts a form of 'realism' which assumes the world described through systematic study is the 'real' world that exists independently of our beliefs and understanding of it (Crotty, 1998; Smith, 1998).

Social sciences came under the influence of 'objectivism' during the nineteenth century, coinciding with the establishment of scientific methods drawn from the natural sciences, with the term 'positivism' being coined by the French philosopher August Comte (Hacking, 1983). Positivist traditions assumed a clear separation of objective facts from subjective values, believing it possible to discover objective and true accounts of both the natural and human social world (Smith, 1998). Social scientists adopted versions of the methods and assumptions of the natural sciences, in an attempt to provide scientific explanations for social relations and processes (Smith, 1998). Positivist approaches typically adopt quantitative approaches which aim to divorce a phenomenon from its context by seeking to minimise or control contextual influences, including subjective biases of the researcher (Crotty, 1998). The aim of this approach is to isolate the effects of a relatively small number of variables, using quantification and statistical tests of significance. Working from this

position, researchers select methods that will reveal a 'true', objective account of reality.

A well-known critic of positivism, Popper (1959; 1963) believed that observation is always shaped by theory and considered the criterion of verifiability as too strong and proposed for it to replaced by a criterion of falsifiability (Smith, 1998; Popper, 1959; 1963). Popper (1959; 1963) argued that it is impossible to verify that a belief is true and that scientists are called upon not to prove a theory, but to try to prove it wrong. Kant (1724 -1804) also had a major influence on the positivist position with his view that there was no absolute description of the world uncontaminated by the observer and that all knowledge is mediated by prior experience (Luchte, 2007; Smith, 1998)

Kuhn (1970) proposed that it is not merely individual theories, but whole worldviews or paradigms involving sets of beliefs or conceptual constructs in which scientists make sense of the world, which must occasionally shift in response to evidence (Crotty, 1998; Kuhn 1970). Kuhn's ideas became the cornerstone of scepticism about scientific truth (Patton, 2002; Crotty, 1998). Rather than seeing scientific inquiry as progressing towards universal truths about nature, he suggested that science is best seen as a series of power struggles between advocates of different worldviews, which are embedded within a set of beliefs, values and techniques shared by that community (Patton, 2002). In the light of these arguments, science was no longer viewed as describing the world passively or objectively; rather it was seen as creating knowledge of the world (Kellner & Lewis, 2007).

Over time 'positivism' and the assumptions about the knowledge associated with it have been challenged and developed in both the natural and social sciences.

Today's more circumspect form of positivism, known as post-positivism refers to probability rather than certainty and claims a degree of objectivity, rather than absolute objectivity (Crotty, 1998). However, due to the complex history underpinning positivism, the term itself and many related terms have attracted some negative connotations and disputed definitions (Patton, 2002). Despite being criticised for being reductionist and failing to consider the influences of context, versions of positivism have been hugely influential in the progression of science and medicine (Smith, 1998). It is no longer considered necessary to go to great lengths to criticise post-positivist assumptions or to set qualitative methodologies against quantitative methods or vice versa.

Few, if any, scientists or researchers today would regard themselves as unreformed positivists, and evolving forms of post-positivism continue to inform much contemporary social science research. Nevertheless, post-positivist assumptions are most typically associated with quantitative methods of enquiry and interpretive assumptions linked to qualitative methods. For instance, within the field of trial recruitment, researchers influenced by post-positivism are more likely to adopt a survey approach to measure dimensions of satisfaction or understanding during recruitment, employing quantitative methods and statistical analysis. However qualitative research may also be informed or directed by post-positivist assumptions (Creswell, 2007 ; Patton, 2002). In practice, for qualitative inquiry, this would mean the incorporation of the language and principles of science into naturalistic inquiry; striving to minimise bias through the adoption of a neutral stance and a belief in an objective truth and concern about validity, reliability and generalisability (Patton, 2002). From this position, interview data may be collected using standard procedures, and the researcher may assume the data will provide reliable accounts of their experiences or access to 'a reality'. However, this approach

can be criticised for not acknowledging the social and cultural contexts in which the accounts are created and understood.

2.1.2 Interpretive paradigms

Comparable to the complex history underpinning positivist traditions is an equally complex history underpinning interpretive traditions. The terms constructionism, constructivism, social constructionism and interpretivism occur in the literature reflecting a range of interrelated concepts and positions underpinning non-positivist paradigms (Ritchie et al., 2014; Merriam, 2009; Crotty, 1998). Nonetheless, a central assumption underpinning these positions is that human beings have evolved the capacity to interpret and construct reality. Therefore the world of human perception, unlike the physical world, is not real in the absolute sense, but meanings and knowledge are constructed by human beings as they engage with the world they are interpreting (Patton, 2002). Interpretation is therefore considered integral to how humans, relate to others and our social existence.

Unlike positivist positions which seek to apply the same rules of knowledge production used to understand the physical word to the social world, interpretivism views the human social world as different from the natural physical world. Therefore the reality and knowledge of this world must be situated differently (Guba & Lincoln, 1994). Consequently, from this theoretical position, the best way to understand or acquire knowledge about the social world of humans is to perceive all knowledge about this world as being socially constructed, as opposed to there being an objective truth, waiting to be discovered (Merriam, 2009; Patton, 2002). Kuhn (1970) applied this assumption of constructed knowledge to every way of knowing, including how we know the physical and natural world. However, in the

context of this thesis, I am focusing on the constructed knowledge only in the context of social sciences, that is, how knowledge of the social world rather than the material world is situated.

The roots of interpretivism as an academic activity predate social constructionism, with two centuries of philosophical dialogue providing a foundation for 'understanding,' which lies at the heart of interpretivism (Patton, 2002). Today's interpretivists have been influenced by many historical and theoretical streams including; hermeneutics, phenomenology and symbolic interaction (Merriam, 2009; Crotty, 1998). Hermeneutics has origins in theology, philosophy and linguistics, and is defined as the theory of interpretation; the hermeneutics introduced the significance of studying the 'lived experiences' of individuals (Smith, 1998). 'Lived experience' refers to meaning that is interpreted and constructed by people in their social and historical context, with the underpinning view that experiences cannot make sense without reference to the context in which they occur (Smith, 1998). The idea here is that the whole can only be understood in terms of the sum of its parts, with the whole being an individual's perception of reality and the parts being the situated or lived experience.

Interpretivism has also been influenced by phenomenology, which originated with Husserl's (1859-1938) attempts to construct a philosophical science of consciousness. Phenomenology involves the study of the social world and the nature of experience (Patton, 2002). This position requires a suspension of presuppositions to allow access to the nature or 'essence' of the so-called lived experience i.e. the objects of our experience before we start thinking about them, interpreting them or attributing meaning to them (Crotty, 1998). Phenomenology, therefore, assumes there is an essence or essences to shared experiences (Patton, 2002).

Symbolic interactionism, another important theoretical movement informing interpretivism, is a social-psychological approach which sees interactions between people and the symbolic meaning and interpretations people attach to their social actions and environments as a means of understanding human behaviour (Blumer, 1969).The process of symbolic interaction embedded within societies is assumed to give rise to our very 'being' - a 'being' that defines us as conscious and self-conscious human beings, where the self is an ever changing 'product' of ongoing interactions (Smith, 1998; Blumer, 1969).

Unlike other philosophical positions, social constructionism cannot be traced back to a single source and has emerged from the combined influence of various philosophical developments (Burr, 2003). The concept of socially constructed knowledge is embedded within all the early interpretive positions, which asserts that there are useful interpretations of the social world, but there is no 'true' or 'valid' interpretation (Crotty, 1998). Even so, it wasn't until Kuhn's (1970) radical notion that socially constructed knowledge could be applied to science, that social constructionism became a highly influential methodological paradigm (Patton, 2002).

A significant contribution to social constructionism is the work of Berger and Luckmann (1966), in which knowledge is viewed as the effect of social processes and practices with individuals experiencing these as if the nature of the world is pre-given or fixed (Burr, 2003; Burger & Luckman, 1966). That is, 'the way things are' is really just 'the sense we make of them'. Social reality is seen as socially constructed, through persons and groups interacting together in a social system over time, with knowledge and meaning becoming embedded in the institutional fabric of life (Berger & Luckmann, 1966). There is no one feature which could be said

to identify a social constructionist position (Burr, 2003). However, this position usually has one of the following key assumptions: a critical stance toward taken-for-granted knowledge; recognition of the historical and cultural specificity of knowledge; recognition that knowledge is sustained by social processes and that knowledge and social actions go together (Gergen, 1985).

More extreme constructionist positions, which argue that true representation is unattainable and everything is socially constructed (Waszak & Sines, 2003), are of limited value if taken too literally. From such an extreme viewpoint, where everything is 'relative' and nothing is known, all concepts and theorising that form the basis of the research question, become social constructs and matters of analytic interest. Therefore, no moral or cultural consensus can ever be reached, and nothing can ever be known (Burr, 2003; Crotty, 1998).

More moderate versions of constructionism embrace a form of realism which acknowledges that human perceptions do provide some kind of knowledge about the world, even if this knowledge is mediated through our senses and we cannot be directly aware of it (Ritchie et al., 2014; Burr, 2003). From this view all forms of knowledge are partial, and a certain degree of relativism is unavoidable. Social constructionism can, therefore, be considered as both realist and relativist, in the sense that even if we accept that reality is a socially constructed reality, this is not to say that reality is not real (Crotty, 1998). We cannot make sense of this world without our perceptions of the world, but these perceptions are informed and most likely originated in our understanding of the social world. Therefore an individual's interpretation of the social world is dependent on the cultural and social context in which they exist, fused with individual variability as to what each of us makes of the social world.

2.1.3 Pragmatism

Pragmatism does not assume a unifying position or methodology which underscores all scientific activities. Rather, it recognises that criteria for 'ways of doing' research change over time and strategies are in place dependent on the objectives that guide research and what is to be achieved (Rorty, 1991). Consequently, providing a precise definition of pragmatism is challenging, reflecting the diverse, evolving range of philosophical positions and rival factions that are characterised as pragmatic (Talisse & Aikin, 2008; Baert; 2005; Crotty, 1998).

Typically referred to as the initiator of pragmatism, Peirce (1931-58) insisted '*pragmatism* is not a worldview but a method of reflexion, having for its purpose to render ideas clear' (Crotty, 1998). In essence, Peirce proposed that to survive, humans develop habits of thought and action to comply with their individual needs (Maxcy, 2003). Pragmatists regard their meta-methodology as neither a 'system' nor a fully formed 'philosophy'. Indeed, they tend to only regard a method as appropriate if it achieves its purpose (Maxcy, 2003). The influence of pragmatism can be seen in the increasing tendency for researchers to use pragmatic criteria for deciding method acceptability rather than epistemological assumptions and associated traditions. With the best method or mix of methods considered to be the one that is most effective (Tashakkori & Teddlie, 2003).

Pragmatism acknowledges the plurality of knowledge and views the social world as a matter of practice, offering justification for the use of research method pluralism, by moving outside of the methodological confines of particular orientation or discipline (Tashakkori and Teddlie, 2003). The influence of pragmatism on social science has enabled projects to be undertaken without the need for prior

identification of what is 'true' or 'valid', allowing researchers to broaden their lens and practicalize (to make practical) their research goals (Maxcy, 2003).

Despite their diversity, all pragmatic approaches share an emphasis on that 'which works out most effectively' (Rescher, 1995). Rorty suggests that philosophical debates should be relinquished if they do not have visible consequences (Rorty, 1990; 1999). Nonetheless pragmatism's reluctance to define itself as a 'school of thought' means that it is open to criticism for its lack of critical rhetoric and theoretical ambivalence (Proctor, 1998). Baert (2005) suggests that abandoning theory altogether is untenable as pragmatists themselves have pointed out that our presuppositions are an essential element of any knowledge. Baert (2005) proposes a version of pragmatism that remains open-minded to presuppositions, recognising that it is better to be aware of our theoretical perspectives rather than deny what cannot be denied.

There is also a reluctance among advocates to label pragmatism as an epistemology, as this way of knowing can provide a useful perspective to navigate through the theoretical complexity which underpins social science research. A pragmatic perspective can also be particularly effective in the field of health care where applied research is necessary, and the need for practical research goals is pressing. Moreover, the adoption of a pragmatic position does not necessarily equate to the relinquishing of schools of thought. Rather, pragmatism can be viewed as a way of ensuring that methodological considerations are rooted in what is most effective for achieving the aims of the research and avoiding what Mason (2002), describes as ' becoming mired in an ultimately self-defeating debate.'

2.2 Positioning my case study

A key assumption underpinning the theoretical positioning of this case study was how I chose to define or perceive clinical trial recruitment and how trial recruitment could be best understood in terms of the aims of my thesis. My thesis was positioned in the context of a grant-funded PhD studentship which formed part the patients' perspective theme of the MRC Hub for Trials Methodology Research. This theme focuses on ensuring the views and experiences of patients are drawn upon to inform the design and conduct of clinical trials. Consequently, my broad objective was to gather empirical evidence in an unexplored area of recruitment to contribute to the existing literature, both conceptually and empirically.

In addition to considering trial recruitment from the perspective of a member of the HUB, I also considered my own assumptions about trial recruitment as a member of society and a user of the health service. I have been approached about two separate clinical studies: an observational study involving the monitoring of my daughter's oxygen levels shortly after birth; and a second involving an RCT of a foetal monitoring system used during labour with my son. From these personal experiences of recruitment, I recognised the significance of the socio-medical context in which recruitment occurs. Moreover, insights gained into the process of recruitment acquired while working on a qualitative study which examined experiences of recruitment in the paediatric context, also influenced my interpretation of the process of recruitment (Shilling et al., 2011). Conducting multi-perspective interviews with individuals with direct experience of recruitment made me aware of the strengths of qualitative inquiry when examining a phenomenon that can only be made real through the fabric of human social life.

In light of these critical reflections, I adopted a moderate position of constructionism, influenced by pragmatism. Aligned with this qualitative tradition of a case study methodology, I viewed this study as an interpretive endeavour with the most important role of the researcher being not to discover an external reality but to construct a clearer picture of the phenomenon under study through integrating interpretations of situation and context (Stake, 1995). From this position, I considered trial recruitment not as something that can be known in an absolute objective sense, but as something that could be known about in the ways 'most of us live our everyday lives, as though reality exists and can be known about' (Oakley, 1999).

Due to case study's focus on a particular situation, context or event, a common criticism of this methodology is its inability to achieve empirical generalisation from sample to population typical of positivist positions. Nonetheless, advocates propose that case study can produce generalisation that is conceptual, therefore having relevance in theoretical development (Merriam, 2009; Yin, 2003). However, in contrast to quantitative research which aims to eliminate or balance out contextual effects, a focus on the 'uniqueness' of individual cases and context are considered essential for the refinement of understanding in case study methodology (Stake, 2003; 1995). Furthermore consistent with a qualitative methodology, in-depth engagement with the complexity of phenomena has the potential to provide new insights enabling the researcher to develop models, typologies and theories as ways of describing and explaining the social world (Flick, 2007; Seale et al., 2004). Due to the lack of robust theory underpinning recruitment research I was interested in the refinement of understanding and conceptual development that can arise from a qualitative case study methodology.

From a position of a qualitative researcher, researching a fundamental component of a principal quantitative methodology underpinning evidence-based medicine, I was aware of the inherent tension between adequate recruitment and the ethical conduct of clinical trials. My epistemological awareness enabled me to position myself outside of this tension. I did not perceive my role as necessarily to directly inform practice to improve recruitment in the sense of the numbers recruited, or to improve the ethical conduct of research. I regarded the purpose of my research to provide a detailed examination of how individuals construct the process of recruitment, providing insights that would help to inform those who are involved in developing, recruitment research, recruitment strategies and practices. A stance influenced by pragmatism allowed me to view my interpretive position as a qualitative researcher as not in opposition or antithetical to the quantitative methodology intrinsic of clinical trials, but as the most effective position to enable me to address my research objective. Pragmatism provided a paradigm that enabled this complexity to be navigated efficiently, avoiding opposition and remaining aware of the need for a multiplicity of forms of health related knowledge.

I considered a case study methodology an important research design applicable to health and social sciences as it can answer complex research questions in which the phenomenon of interest is very closely embedded within the context while addressing the holistic nature of care and treatment (Simmons, 2009; Luck et al., 2006). I, therefore, chose an exploratory qualitative case study methodology, considering this open, flexible methodology as the most appropriate design for the purposes of the study. I believed this methodology would provide meaningful insights into personal experiences of recruitment while acknowledging that human experience is mediated, historically, culturally and linguistically and that multiple realities exist. I viewed the aim of this qualitative case methodology to gain insights

into factors that were significant to individuals' construction of trial recruitment and what factors they viewed as influential to both their satisfaction with this process and their subsequent participation decision.

2.2.1 The 'case' of cystic fibrosis

The clinical context of cystic fibrosis provided the parameter of the 'case', which was jointly agreed between the HUB management team, the local Clinical Trial Research Centre (CTRC), CF experts in the field, my PhD supervisors and myself. Comparison was an important design aspect of this qualitative case study both due to lack of research comparing recruitment experiences across child and adult settings, combined with the recognition that comparison within qualitative methodology forms an important analytical tool used to develop, insight into complex social phenomena (Bradley et al., 2007). CF presented both an underrepresented population in the recruitment literature and an ideal case in which to examine recruitment experiences across child and adult settings, with specialist paediatric and adult CF centres in operation across the UK. Consequently, it was anticipated that this healthcare context would enable me to gain insights into a diverse range of trial experiences including novel and earlier phase trials, older individuals and parents of infants. Furthermore corresponding with my period of data collection a phase IV CF clinical trial was currently recruiting. This trial provided the opportunity to examine recent trial recruitment experiences, particularly in the paediatric context where the majority of this trial eligibility was anticipated to occur.

2.2.2 A qualitative methodology

Case study, located within a broadly constructionist position, consistent with other forms of qualitative methodology, is concerned with specifying and studying individual phenomena in detail, focusing on personal views and circumstances (Thomas, 2011b; Merriam, 2009; Willig, 2008). As I was concerned with how trial recruitment is interpreted, experienced, or constituted, I considered a qualitative methodology as essential to achieving this aim (Merriam, 2009 ; Flick, 2007; Mason, 2002). I sought to understand and unpick how people construct trial recruitment in terms that are meaningful and that offer in-depth insight into this challenging phenomenon.

Case studies do not claim any specific data collection methods but, rather, focuses on achieving holistic explanations of the issue or phenomena under investigation (Merriam, 2009; Stake, 2003, 1995). Nonetheless interviewing is perhaps the most widely used method in qualitative research and is frequently used in case studies (Merriam, 2009; Seale et al., 2004). While single perspective interviewing is commonly employed in qualitative studies, multiple perspective interviewing has the potential to generate a richer understanding and to provide additional insights through studying the discrepancies and convergences in the views of different parties (Kendall et al., 2009). Furthermore, previous studies on recruitment, which have tended to rely on one−dimensional accounts of recruitment (e.g. Quinn et al, 2011; Henzlova et al., 1994), offer limited insights into the relationships between parties and the wider context of recruitment. Multi-perspective qualitative interviews are particularly valuable when seeking to understand the relationships and dynamics among patients with long-term conditions, families and practitioners, and similarities and differences across the needs and concerns of these different groups (Kendall et al., 2009).

I recognised that alternative methods were available, for example, observational techniques, narrative or fully structured interviews. Observational methods may be favoured as a way of examining recruitment as it is 'naturally occurring' avoiding the use of 'contrivances' such as interviewing (Potter, 2002). Nonetheless, distinctions made between natural and contrived methods are considered over simplistic and observational data is still mediated by factors such as the presence or the position of the researcher and recording equipment and the knowledge that the observation is being conducted (Silverman, 2006). Also, within the context of this study, observational data would have provided little insight into how an individual constructs or makes sense of this process, which was the purpose of this study.

A more open narrative method to interviewing could have been selected as an alternative to semi-structured. This style of interviewing is designed to provide an opportunity for the informant to give a detailed narrative account of a particular experience with minimal prompting (Murray, 2015). Narrative methods appear more relevant for gaining insights into personal existential life events or processes which are temporally structured, such as living with illness or the experience of ageing (e.g. Becker, 1999; Pejlert et al., 1999; Reissman, 1990). Recruitment, in contrast, is not existential, but a form of clinical communication embedded in particular institutional discourse. Therefore, very open narrative methods may not produce the most insightful accounts. In contrast, highly structured interview methods involving fixed-choice answers would not enable informants to take the lead regarding what is important to them. Influenced by pragmatism balancing ethical, methodological and practical considerations the most effective choice of design was considered to be multi-perspective, in-depth semi-structured interview. From a constructionist position, I viewed interviews not as accounts that are true or false descriptions of 'reality' but as constructed and constructive versions of events

and inner psychological worlds produced in discourse (Sliverman, 2006; Potter & Wetherall, 1987).

2.3 Quality in qualitative research

The debate on quality in qualitative research is diverse and unresolved and parallels the diverse, evolving historical epistemology underpinning social science research, discussed previously in this chapter. Assumptions about what an individual considers as knowledge are embroiled with conceptualisations of quality. How we know and perceive quality depends on our epistemological position and many of the debates around perceptions' of quality map onto individual debates about the nature of knowledge. In contrast in the domain of quantitative social science research unified standardised procedures have evolved to provide quality assurance procedures which are mostly rooted in positivist epistemology (Reynolds et al., 2011). Concepts of reliability, validity, (statistical) generalizability and objectivity, developed in the natural sciences as criteria with which to judge quality, have been extended for use in quantitative social sciences (Ritchie et al., 2014; Winter, 2000). However, this criterion used in quantitative methods are not considered appropriate for most qualitative research (Yardley, 2000; 2015) although debate still exists around this issue and there is no unified approach for assessing the quality of qualitative research (Reynolds et al., 2011).

However, many qualitative researchers have accepted the need for some criteria for judging the quality of qualitative research (Reynolds et al., 2011). Dixon-Woods et al. (2004) identified over 100 sets of proposals on this topic with many of these adopting conflicting ideologies. On reviewing this literature, Reynolds et al. (2011) identified two prominent discourses. The first focusing on the assessment of quality

as being linked to specific sets of criteria or checklist detailing specific methods or techniques deemed as indicators of quality. This approach appears to have been shaped by post-positivist requirements embraced with the social movement of evidence-based medicine, with the introduction of Lincoln and Guba's (1985) criteria for establishing trustworthiness in qualitative inquiry (Reynolds., 2011; Barbour, 2003; Mays & Pope). Typical criteria include respondent validation, multiple coders, and deviant case analysis. The second discourse identifies quality in terms of the research process reflecting an internal set of values inherent in qualitative inquiry. Common values included: reflexivity, transparency, comprehensiveness, and a systematic approach. This approach advocates researcher-led principles of good practice and questions how far externally determined constructs of quality and predetermined techniques can assure quality (Reynolds et al, 2011;Tracy, 2010).

Advocates of case studies adopting a post-positivist position are drawn to the first discourse on quality, influenced by the criteria originating from the natural sciences (Brown, 2008; Yin; 2009). In contrast, supporters of an interpretive approach to case studies are drawn to the second discourse, acknowledging the centrality of the researcher's role in building a clearer view of the phenomenon under investigation (Merriam, 2009; Brown, 2008, Stake, 1995). The latter position accepts that a researcher cannot be neutral, or objective, or detached from the evidence they are generating, and requires that they seek to understand and make transparent their role in the research process (Thomas, 2011a; Merriam, 2009; Mason, 2002). Consequently striving to remain critically aware of personal values, preconceptions and socially derived frames of reference in this way has been termed reflexivity or reflective practice and is considered central to meaningful interpretive inquiry (Seale et al., 2004; Patton, 2002; Mason, 2002). The very process of research is viewed

as an interpretive activity, with the researcher playing the role of interpreter and constructor of knowledge. Qualitative research acknowledges that the orientations of the researcher are shaped by their socio-historical locations and that social research cannot be unaffected by social processes and personal characteristics (Ritchie et al., 2014; Stake, 1995). Researchers are therefore perceived as active participants' in the research process and in this way the researcher is someone who, like research participants, is actively making sense of the world (Charmaz, 2004; 1996). Similarly, far from regarding experiential data as a potential bias to be removed, Strauss (1987) saw various kinds of personal experience as central to different stages of analysis and maintained that personal experience was integral to researchers being able to generate relevant research questions and uncover valuable insights.

I positioned my judgement of quality from an interpretive framework in which I sought to understand and make transparent my role in the research process (Mason, 2002). I accepted as a qualitative researcher that I was both the subject and object of the research process. I viewed the process of research as an interpretive activity, with the researcher playing the role of interpreter and constructor of knowledge. I, therefore, ensured I maintained a process of reflexivity or critical engagement throughout the research process while recognising the value of my own experiential data (Mason, 2002). Rather than viewing my own experiences as a potential bias to be removed I viewed these experiences as an important methodological tool (Strauss, 1987).

My overall aim was to represent this 'case' of recruitment with a narrative, reflective, tone while complying with the necessary methodological conventions of systematic research (Merriam, 2009; Stake, 1995; 2003). From this moderate

constructionist position, I viewed the criteria for judging either reality or validity as not absolutist but derived from community consensus about what is useful and has meaning (Guba & Lincoln, 2008). Moreover, from a constructionist position, it may be assumed that it is the reader of the research, not the researcher who ultimately determines what applies to his or her context.

2.4 Sampling

Like much qualitative research, qualitative variants of case studies usually draw a purposive sample aimed at capturing the character and diversity of the phenomenon in question (Stake, 2003). In contrast to probability sampling, purposive sampling aims to discover, understand and gain insights into the area of interest (Merriam, 2009). The sampling of cases which are 'information rich' with regards to the focus of the study is considered to be of central importance to purposeful sampling (Patton, 2002). Nonetheless, sampling remains one of the complex dilemmas in research design that qualitative researchers face, and there is no 'one size fits all' solution to the problem (Barbour, 2001).

Also similar to qualitative research within qualitative variants of case study a predefined sample is not always appropriate or meaningful. Advocates of the case study acknowledge that how much and how long the complexities of the case should be explored involves a strategic decision and that the researcher must acknowledge that not everything about the case can be understood (Stake, 2003). Within much qualitative research 'theoretical saturation' or the point when no new insights would be obtained from further sampling (Charmaz, 2006; Glaser & Strauss, 1967), is used to guide when data collection should cease. Nonetheless, there are no specific rules to guide theoretical saturation or whether it can actually

be achieved in practice (Charmaz, 2006; 1990). To pragmatically address the difficulty of achieving theoretical saturation or knowing everything about the case I considered an appropriate sample size for this study to be one that enabled me to adequately answer the research question and put my case forwards (Marshall, 1996).

2.5 Analysis

An important difference between case study and other qualitative methodologies is that the case study can be both inductive and deductive, and as such, can be useful to test and extend existing theories (Thomas, 2011; Yin, 2009). Equally, it can be a useful strategy where there is no strong theory on which to base a study. Initial questions can be developed, changed, refined or deleted as the study progresses, and in the light of new findings from the data. A comparative focus is a powerful conceptual, analytical mechanism often adopted within a case study methodology and indeed in qualitative research in general. Nevertheless, a strong comparative focus within case study research may at times compete with learning about a particular case (Stake, 2003).

A case study is not strictly attached to a specific paradigm and multiple methods of data analysis are characteristic. Consequently this approach draws on the range of analytical strategies which have evolved from the diverse range of disciplines underpinning qualitative inquiry. Analysis is primarily led by the nature of the case and the purpose of the research. Multiple methods of data analysis are characteristic within a case study and 'analytical eclecticism' is typical (Thomas, 2011b).

Pluralistic approaches to qualitative analysis aim to address the difficulty of balancing meaningful interpretations of personal 'narrative life world' accounts with broader 'sociological world' accounts (Frost, 2011; Thomas, 2011b; Conrad, 1990). With a concern that focusing on border patterns in which the data are only coded conceptually has the potential to 'disembody' the data from the context in which it was co-constructed with the interviewer (Frost, 2011; Conrad, 1990). Conversely, there is a concern that focusing on the finer details of individual perspectives may be at the expense of losing conceptual or theoretical strength of the analysis (Thomas, 2011; Conrad, 1990). By examining data from different analytical positions, the impact of assumptions and limitations associated with viewing the data from one perspective is reduced (Frost, 2011).

Analysis of qualitative data has been described as a blend of art and science, involving a process of breaking down the corpus of data into its constituents parts, and through the reassembly, one gains a detailed understanding of the integrity of the whole (Schwandt,2001). The exact balance of art and science and the distinction made between analysis and interpretations varies according to differing epistemologies. Although 'the art of understanding' is not fully definable in terms of procedural steps, what is common across approaches is the recursive practice of sorting, organising and reducing data into something manageable, combined with the exploration of ways to reassemble the data to assist in the process of interpretation and 'the art of understanding' (Schwandt, 2001).

Grounded theory is one of the most cited methodologies in qualitative inquiry in medical research and the 'constant comparative' method, a fundamental part of this approach, has become a central method of many interpretive, analytical processes including case study (Thomas, 2011; Bryant & Charmaz, 2007). Despite some

grounded theory work being criticised for not adhering to all the principles laid down by its founders (Dixon-Woods et al., 2007; Barbour, 2001), much research from an interpretive position adopts components or different combinations of these elements without claiming to adopt a grounded theory methodology. While it is beyond the scope of my thesis to provide a full critique of grounded theory, it is important to recognise the significance of this approach in informing much contemporary forms of qualitative analysis today. Since its inception (Glaser & Strauss, 1967), grounded theory methodology has evolved into diverse forms (e.g. Charmaz, 2006; Strauss & Corbin 1998) with the original authors diverging in their interpretations of the methodology, they jointly created. Within earlier versions of grounded theory, the influence of post- positivism is more notable (Glaser & Strauss, 1967), with later versions more in keeping with constructionist principles (Charmaz, 2006; Strauss & Corbin 1998).

Grounded theory emphasises inductive analysis, with analysis and data collection coinciding, involving an iterative process designed to advance the developing theory (Charmaz, 2006; Glaser & Strauss, 1967). Data analysis involves breaking the data down into labeled components or 'codes' that are continually compared within and across interviews (constant comparative method). The process of coding is central to most qualitative analysis, and it is during this process of coding and comparing that the researcher begins to define what is happening in the data, and 'to grapple with what it means' (Charmaz, 2006). This grappling appears to be synonymous with the delicate balance of art and science, the intuitive and systematic procedures inherent in the process of interpretation in much qualitative inquiry.

While I recognized the value of breaking the data down to gain a detailed conceptual understanding, from a constructionist position I also the recognized the value of discursive approaches to analysis which aim to highlight the ways in which 'knowledge' is 'socially constructed' (Holt, 2011, Potter & Wetherell, 1987). Discursive approaches are underpinned by a constructionist ontology which aims to address hidden assumptions and taken-for granted knowledge (Holt, 2011; Burr, 2003). This approach emphasises the consequential nature of accounts in which meaning is viewed as being constructed from our engagement in the world rather than discovered (Potter & Wetherell, 1987). Rather than viewing language as a means to access 'the truth' constructionist approaches recognize that it is through language that meanings are negotiated and 'realities' are produced (Holt, 2011).

Charmaz (2006) has developed a grounded theory approach aligned with constructionist principles which are considered compatible with discourse analysis methods and it is from this position I aimed to approach my analysis. In line with key assumptions of a position of social constructionism and a qualitative case study methodology my approach to analysis was interpretive, flexible and pluralistic (Frost, 2011; Thomas, 2011). I avoided imposing a particular strategy of interpretation on the data that risked losing important facets or components of the data. Instead, I drew on analytical methods that were most suited to the type of data generated and most able to address the research aim.

I aimed to examine the data conceptually, drawing on elements of grounded theory without claiming to adopt a formal grounded theory methodology (Charmaz, 2008; 2006). From a constructionist position, I did not view analysis as a passive process with themes or concepts simply 'emerging' from the data. Rather I recognised that I, in effect, created themes or conceptual categories to help make sense of the

meanings in the data and construct a comprehensive account of the 'case'. In addition I aimed to draw on aspects of discursive forms of analysis to ensure that the contexts of themes occurring in the data were not lost and any contradictions, ambiguities and tensions within individual accounts were captured (Holt, 2011; Potter & Wetherell, 1987). I therefore aimed to adopt a pluralistic approach to increase the integrity of the interpretation and to help reduce the likelihood of my assumptions dominating interpretations, rather than the participant's construction leading the story (Frost, 2011). I aimed to capture the integrity of the data by capturing the context in which it was produced, whilst also interpreting the data conceptually (Charmaz, 2006)

2.6 Summary

Within this chapter, I have discussed the choice of a qualitative case study methodology which was adopted from a moderate constructionist position influenced by pragmatism. Central to my research focus was the importance of the individual perspective, both as 'potential participant' 'parent of potential participant' and 'recruiter'. However rather than defining these roles according to the legislative and ethical guidelines I aimed to make the concept of recruitment connect to the accounts of people with direct experience of the process. Within the next chapter, I will outline in detail the methods that were chosen in order to address the research aims.

CHAPTER 3: METHODS

3.0 Introduction

A qualitative case study in cystic fibrosis was carried out to examine recruitment experiences across adult and child settings, involving perspectives from both sides of the exchange-those being recruited and those doing the recruiting. In this section I describe the design of the study where methods were selected and adapted within the framework of the qualitative case study.

3.1 Research aim and objectives

Aim

To conduct an exploratory qualitative case study, with a comparative focus across adult and child settings, to further empirical and conceptual understanding of the process of trial recruitment

Objectives

- To use in-depth, semi-structured interviews to explore perspectives on trial recruitment for children (and their parents), adults and practitioners.
- To examine divergences and convergences across accounts from within the subgroups: children (and their parents), adults and practitioners.
- To explore issues contributing to positive and negative recruitment experiences.
- To identify common elements in how individuals make sense of trial recruitment.

3.2 The research setting

In order to achieve the research aim of this study, I needed to engage with patients and practitioners working within the context of CF care in the UK. People with CF are treated within tertiary centres which comprise part of the 'specialist services'[3] within the NHS. These specialist services are defined nationally according to the Specialised Services National Definition Set (SSNDS), which has been drawn up to identify and ensure provision of care within the NHS for children and adults with rare diseases or disorders (NSCG, 2010). According to this definition, a service is considered specialised if the catchment area for that service is greater than one million, which means that CF specialised care is not provided by every hospital in the UK. Therefore specialist CF centres usually have an active caseload of over 100 patients, with adult centres often exceeding 150.

At the time of this study, there were 24 adult and 24 paediatric specialist CF centres in the UK. These centres provide and oversee care to people with CF depending on the individual's needs and circumstances. For instance, this care may be provided in the form of 'shared-care' between the local hospital and the nearest specialist CF centre, where the individual does not live a convenient distance from the specialist centre. Consequently, early sampling decisions involved the selection of specialist CF centres from which to recruit adults, families and practitioners.

[3] Specialist services are services which have been designed and commissioned to improve the lives of children and adults with rare health conditions, which include 34 definitions of relevant conditions and treatment classifications (NSCG, 2010).

As these CF centres were part of the health care provision of NHS England, I required informal approval from the centre CF teams and local formal Research and Development (R&D) approval. Initial concern was expressed from the MCRN Study Assessments Committee that CF patients were already "heavily researched", so the committee needed to be assured of both the sensitive management of the study and the potential value of findings for practitioners and patients. The sampling of CF centres was therefore guided closely by experts in the field which included; CF specialists, the local clinical trial team, involved in setting up a national CF trial (TORPEDO-CF), the NIHR Comprehensive Research Network and the MCRN Local Research Networks (LRNs).

Through collaboration with these experts, the number of informants recruited from each centre was kept low, to reduce the research burden on participating centres, with the additional advantage of introducing variability of CF centres across the overall sample. It was therefore proposed that the study would run at four adult and four paediatric CF centres across four regions in England. Where possible, I approached adult and paediatric CF centres within the same geographical location/city in the first instance. I considered the study to be a multi-sited or a collective case, as opposed to a multiple case study, where the intention was not to compare recruitment experiences across different CF centres (Baxter & Jack, 2008).

At each CF centre, a senior CF clinician was invited to act as the clinical lead for the study. Once this had been agreed, further negotiations began with the CF team and associated researchers about the details of the study including aims, objectives and centre requirements regarding informant identification. Practitioners at each CF centre were invited to attend a presentation about the study. This enabled them to voice any suggestions and concerns and adapt the study accordingly. It also

provided me with a first-hand opportunity to describe the study in detail, distribute necessary study documentation and where appropriate, provide reassurance and guidance regarding the focus of the research.

These access negotiations with practitioners involved a protracted process of mediation. I maintained an honest, open position, drawing on my professional and personal skills and experience, to establish rapport and trust with practitioners. I strove to maintain this trust throughout the study and beyond. Initial negotiations were the most difficult, as practitioners were most likely to potentially feel under scrutiny in relation to their recruitment practices, and protective of 'their' client group, acting as 'gatekeepers' to potentially vulnerable informants.

3.3 Sampling for semi-structured interviews

For the patient and parent sample a combination of consecutive and purposive sampling was used. Consecutive sampling aimed to avoid practitioners selecting patients or families who they thought would agree and purposive sampling was used to encompass diversity. This strategy involved actively selecting the most productive sample by its relevance to the research question (Mason, 2002; Marshall, 1996). The aim was not to generate a representative sample (often the aim of quantitative research pursuing 'generalisation'), but rather to capture variability to support analytical generalisation or theoretical elaboration. This type of generalisation attempts to link findings from a particular 'case' to develop or elaborate theoretical concepts that may have relevance to settings beyond that studied (Scwhandt, 2007). Practitioners were sampled purposively to capture diversity in both professional status and research experience and were invited to

participate by myself during site visits or via the Principle Investigator (PI) at each CF centre.

The sampling strategy was stratified according to 6 respondent groups.

- Adults with CF
- Parents of children with CF <7 years
- Parents of children with CF ≥ 7 years
- Children with CF aged ≥ 7 years
- Paediatric practitioners
- Adult practitioners

Within each of these sub-groups, I aimed to sample informants with a broad spectrum of views and experiences. For the patient sub-sample, I sought to include individuals with different clinical research experiences including those who had declined participation; those who had accepted; those who were found to be ineligible; those who had withdrawn from a trial or study, and; those who were non-eligible. I also aimed to sample patients of a range of ages including young and older adults, parents of infants and children (too young to be interviewed) and children of diverse ages. It was felt that only children aged 7 and older could reasonably be approached about the study, due to the nature of the research and the complex concepts involved.

For the practitioner sample, I aimed to sample practitioners with a range of recruitment experiences including those with direct trial experiences in the CF context, including both nurses and clinicians. By selecting a diverse sample both within and across these sub-groups, the aim was to identify central concepts which were able to cut across this variety. The sampling criteria were in part predefined

and in part developed iteratively in the light of findings in the data and the provisional analysis and interpretation of the data. For example, during my analysis of the early interviews, I found that some informants appeared to speak of intrinsically valuing being offered research, describing how they had felt glad to have been asked to consider participation, despite declining. Based on some practitioners' perceptions of the CF patient group as being 'heavily researched', I had anticipated that it would be more likely for patients to construct being approached about trials as a potential burden. To explore the concept of research as both a potential burden and the value of being asked I was keen to sample patients who had not recently been invited to participate in a clinical trial or who had never been asked, to gain insights into the circumstances that might influence how individuals experienced the invitation. This sampling criterion was not part of my initial sampling strategy, which was to focus on patients who had been recently approached about a clinical trial. This refinement of the sampling criteria during the study was in line with the goal to sample respondents with a broad and diverse range of experiences.

3.3.1 Sample size

In collaboration with my supervisors, based on their prior experience and the comparative focus of this study, it was anticipated that a minimum sample of N=48 (16 adult patients, 16 patient families and 16 practitioners) would be both achievable within the time constraints and adequate to address the research aim. To address the comparative aims of the study, I aimed to recruit patients and practitioners from adult and paediatric centres, with approximately equal numbers from each.

3.4 Recruitment to this study

Recruitment to this study was dependent on participating CF centres acting as patient identification centers (PICs) which required a continuous process of collaboration with each participating centre throughout the data collection phase. Patients and parents of child patients were invited to consider participation in this study either by members of the CF team or members of the local research network (LRN), depending on the resources available and procedures in place at each centre. I collaborated closely with the CF clinical team or the LRN team at each participating centre to develop a suggested guideline for introducing CACE.

A practitioner introduced this study as a separate interview study, which is entirely independent from the CF centre and clinical research conducted at the centre. A recruitment log was also provided to enable centres to keep a record of the number of patients that were approached which would provide insights into the sample characteristics and the acceptability of this qualitative study.

If the patient/parent was interested in the study, the practitioner gave them a CACE recruitment pack (containing an introductory letter, a CACE informant information leaflet, consent form, a reply slip and a Stamped Addressed Envelope). Personal contact details were passed onto me only after potential informants had expressed an interest in the study and given permission for me to contact them. Alternatively, the family completed the reply slip containing their contact details and returned in a stamped addressed envelope. These alternative methods provided practitioners with flexibility in their approach, according to individual patients and parents' needs and circumstances at the time.

I liaised closely with CF teams at each centre regarding the most appropriate time to contact patients and their families according to the team's judgement, allowing me to be sensitive in timing my approach to patients and families. Practitioners were invited to participate in the study either by myself during site visits or via the Principal Investigator (PI) at each participating CF centre.

3.5 Ethical considerations

3.5.1 Approval requirements

This study required contact with NHS patients and practitioners, hence approval was sought via the National Research Ethics Service (NRES), through the Integrated Research Application Process (IRAS) and approval was given 20th August 2010 by the North West 9 Research Ethics Committee (REC) (ref.10/H1014/41) In addition, Management permission ("R&D approval") was obtained from each participating NHS Hospital Trust. To assist in the R&D approval process and ensure adequate support and management of the study, the study gained (NIHR) portfolio adoption (NIHR CSP Ref. 53231) and MCRN adoption.

The study was carried out within the guidelines of the NHS Research Governance Framework HRA, 2015; DOH, 2005). The study also complied with the Data Protection Act of 1998 concerning the handling, processing and storage of the study data (Legislation.gov.uk. 2015). Rigorous steps were undertaken to avoid any breach of confidentiality including anonymisation of data, secure transfer and storage of audio−recordings, removal of personal details from transcripts and secure storage of all study materials bearing informants' contact or other personal details.

3.5.2 Service user involvement

In the context of this study service users were the children, their parents and adult patients attending CF centres in the UK. To ensure that the views of these groups informed the study design, service user involvement was sought throughout the study duration. This engagement was achieved through liaison with a CF Trust Expert Patient Adviser and a local Young Person Advisory Group with the support of the MCRN Consumer Liaison Officer. The Clinical Director of a local Paediatric CF Networks also acted as a co-investigator for the study, providing important practitioner involvement along with clinical expertise and knowledge in the area of CF. I also liaised closely with and received important feedback from the local clinical trial team involved in setting up a national CF trial (TORPEDO-CF) and each local participating CF centre throughout the duration of the study.

This liaison focused on:

i) the study design, including views on Patient Information Leaflets
ii) data collection and conduct of the research, including ongoing feedback on interview guide
iii) assistance and guidance on the dissemination

Together this extended period of collaboration with service users and experts in the field helped ensure the study's design and conduct were sensitive to the needs of potential informants and the findings were the most meaningful for those concerned.

3.5.3 Risks, burdens and benefits

Throughout the study, the needs of potential informants, both patients and practitioners, were always put first before the needs of the study. I regarded an empathetic stance as ethically essential and also important in gaining and maintaining trust and rapport with patients and practitioners, which was critical to the success of the study. I remained sensitive to the possibility that the time and energy of all informants, particularly patients', would be limited. Therefore I always ensured that there was considerable flexibility regarding the time and place of our meetings, to help minimise any potential burden of the study on informants. Interviews with patients and parents either took place in their homes or at a place of their choosing and at a time and date that was most convenient for them.

The aim of this study was to provide insights into how individuals made sense of the process of recruitment and though this study did not claim that there would be a direct benefit for informants, it did allow imformants opportunity to air their views and to reflect on their experiences (Scott et al., 2002). Also as part of the study design, all informants were offered summaries of the main findings. While I recognised that taking part in an interview may bring some quite strong emotions to the surface for some informants, I also anticipated this risk was minimised due to the focus of the interview. In addition, I always signalled to informants that they had control over the interview and could decline to answer any questions if they wished, or stop the interview at any point. Guidelines adopted by the RECRUIT study (Shilling et al. 2011) were also in place for managing informants whose level of distress gave cause for concern.

I had prior experience of conducting qualitative research in trial recruitment, having worked on the RECRUIT methodology study (Shilling et al., 2011) (in the context of four paediatric trials in both chronic and acute specialities) for over 12 months. I am also a qualified mental health nurse with nine years' post qualification experience of working in highly sensitive and challenging clinical and research situations. I also received regular supervision and support from my supervisors who have extensive knowledge and expertise in health related studies and qualitative research.

3.5.4 Informed consent

Key ethical requirements within this project were the maintenance of the rights and safety of all informants, including the preservation of freely given consent. All potential informants were provided with a study Information leaflet (see Appendix 2 for an example of a study information leaflet) which was designed according to the different requirements of the participating parties (i.e. children, young persons, parents, adults and practitioners). Before informants were asked to complete the consent form, I ensured that they were aware of: the voluntary nature of participation; and the study's independence from their CF team and any clinical trial or studies they may have participated in, what the study would involve and what would happen to the information they provided (including audio recordings of the interview and anonymisation of data).

Maintaining independence from the CF centres was important to ensure informants did not feel under any obligation to participate and that they felt they could speak freely about any CF trials they had been approached about. Consent was obtained from the parents or guardians in addition to obtaining assent or consent (depending

on the abilities) of the child/young person involved. Separate Information leaflets, assent and consent forms were designed for younger (7-10 years) and older children (11-15 years). The groups mapped onto the primary and secondary school division, but I used the age brackets flexibly and always took along all sets of information leaflets, and the child/young person then selected the leaflet they decided was most appropriate for them. This process was particularly important for older children, as some teenagers preferred the adult information leaflet.

3.6 Data collection

3.6.1 Multi-perspective qualitative interviewing

In -depth, semi-structured interviews were used to explore perspectives on trial recruitment for children (and their parents), adults and practitioners. I recognised the need for some structure in order to be able to address my research aims (Silverman, 2006; Rapley, 2007). Consequently, the trajectory that each interview took was based on an interview guide (discussed further in section 3.6.2) that was developed for each group of informants.

Despite some structure, my interviews aimed to elicit where possible a narrative account of recruitment experiences, as well as informants' specific views about certain aspects of clinical trials and clinical research (depending on individual experience). Flick (2014) has termed this approach, the episodic interview, in which individuals are encouraged to tell stories about particular experiences in question and answer sequences. This method enabled informants to pursue what they felt was most relevant, while ensuring that specific topic areas were explored. Due to the semi-structured quality of the interviews, it was not considered appropriate to base my analysis upon quantification of the data (Ritchie et al, 2014; Kitzinger &

Willmott, 2002). Instead I was interested in informants' qualitative experiences of trial recruitment and in the issues' they raised in relation to this process.

Basic demographic details were also collected for each informant and audio-recording of the interviews was necessary to ensure adequate capture of informants'' accounts. These recordings were made digitally and were encrypted and transferred from local sites on laptop computers while awaiting transcription.

3.6.2 Development of interview guides

I viewed the research interview for this study as an extended conversation in which I aimed to establish rapport with informants' so they felt comfortable and able to share their perspectives on trial recruitment. I also recognised that within the research context this extended conversation also had distinct qualities which included:

- To maintain an awareness of my effect on the interview (reflexivity)
- To elicit experiences of informants view and experiences.
- To maintain continuity and clarify meaning
- To keep on topic while maintaining depth and clarity (Rubin & Rubin, 2005)

To help ensure the interviews covered the topics necessary to meet my research objectives, I developed a set of interview guides (Mason, 2002) by reviewing the literature, my past experiences in qualitative interviewing in the field of trial recruitment (Shilling et al., 2011), collaboration with experts in the field, including my supervisors, CF specialists, and expert patient advisors. I developed a separate topic guide for each of the participating groups – adult patients, young people,

children, parents and practitioners (see Appendix 3 for an example of an interview guide). The latter guide was adapted according to whether the informant was based in an adult or paediatric setting.

These guides were semi-structured to help me to keep on topic while ensuring enough flexibility to achieve a comprehensive, authentic account of informants' experiences. The interview guide comprised mainly open questions and included suggested wording of questions and potential prompts. At the beginning of each interview, I aimed to elicit informants' broad conceptions, prior knowledge and experience of clinical research. From here, I was able to adapt the questioning according to their research and trial experiences. For individuals who had been approached about a specific clinical trial or trial(s), I also elicited their narrative descriptions of the trial and their construction of the recruitment process, allowing them to voice their concerns and priorities**.** I also explored what individuals expected of the recruitment consultation, how they constructed these consultations, and how they described the decision-making process involved. For individuals who had been involved in more than one clinical trial or study the informant chose which instance they would like to focus on initially. They then typically discussed other trials or clinical research experiences according to their priorities or concerns.

For parents of child patients, I explored how the parents negotiated the child's involvement and how they viewed their responsibilities in this context. For children, I explored their feelings about particular aspects of the trial and how they made sense of the process and what factors they viewed as notable (for more details on interviewing children and young people see below). Interviews with practitioners followed a similar course to the patient interviews, exploring their perceptions of trial recruitment and their concerns and priorities.

3.6.3 Interviewing children and young people

It was intended that where possible parents and children would be interviewed separately, ideally with parents being close but not actively involved (Irwin & Johnson, 2005). This was to avoid the difficulties of interpreting individual experiences from data collected at joint interviews and to ensure each informant's views were accessed. However, during initial data collection I recognised the value of allowing families to negotiate the structure of interviews according to their own needs and preferences. Often parents did encourage their child to be interviewed separately, while they remained nearby and available. However, at other times parents and children indicated a preference for joint interviews. Both the negotiation process prior to the interview, and how the interview process was navigated between parents and child, provided valuable additional insights into family relationships (Kendall et al., 2009). Furthermore, these joint interviews enabled parents to help prompt children to expand on specific issues or experiences.

I recognised that building rapport with young children takes time and that being able to meet a child on more than one occasions is conducive to the establishment of rapport (Irwin & Johnson, 2005; Balen et al., 2000/2001). Unfortunately this was not logistically possible due to time constraints. Alternatives include forms of play-drawing, role-playing, and using props to assist in the establishment of rapport (Irwin & Johnson, 2005). Therefore before interviewing, I liaised with parents with regards to what might help enhance their child's involvement and ease during the interview, for example, if their child liked drawing. The approach to interviewing was also always negotiated directly with the child and adapted to their specific needs and preferences at that time.

For younger children, I used a task-based 'getting to know you' activity to help reassure children that taking part in the interview was about their views and thoughts, not a matter of right or wrong answers (Punch, 2002; Hill, et al., 1996). I invited younger children to write down four likes and dislikes on a spidergram[4] shaped like a friendly spider with "googly"' craft eyes, which children appeared to find amusing and reassuring. I found it helpful in establishing rapport if I also completed a spidergram listing some of my likes and dislikes. I also invited children to ask questions about the study or myself which helped to put them at ease. In addition, before the interview I also encouraged younger children to try-out out the digital recorder, and used this act of recording and listening to their voice to help establish rapport (Ross et al., 1984). I also invited children to take charge of turning the recorder on and off, which gave them a sense of some control over the situation (Mahon et al., 1996).

I developed two prompt guides; a simplified version of the parent prompt guide (aimed at older children) and a set of question cards (aimed at younger children). I invited the child to decide which format they would prefer and children aged below ten years opted for the card format. The set of question cards had a simple, self-contained question relating to taking part in research on one side and a familiar picture of an everyday object or animal and on the other. The sight of these pictures usually made the children laugh or smile, and their familiarity and simplicity appeared reassuring. The cards were laid on the floor, picture side up, and the child was asked to pick up the card with a certain picture and was invited to either read the question or request that I read it. The advantage of this approach was that it

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A spidergram (or spider diagram) is a drawing similar to a mind map, showing a summary of facts or ideas (Punch et al., 2002)

provided the child with a guaranteed degree of control and a sense of involvement and ownership in the research process from the beginning. A one-to-one interview with an unfamiliar adult activity is an unusual activity for younger children (Balen et al., 2000/2001), so this method helped move away from a more formal interview style and engaged the child quickly with the identification of familiar objects. The child was also able to see clearly what was expected of them.

3.6.4 Transcription

Various conventions exist for transforming spoken text into written words, and these conventions are associated with specific forms of analysis, influenced by different methodological and theoretical positions (Lapadat & Lindsay, 1999; Braun & Clarke, 2006). Therefore the choice a researcher makes about transcription in part determines what interpretations can be drawn from the text. Consequently, it is important the transcription process suits the purpose of the analysis (Lapadat & Lindsay, 1999). From a social constructionist position, I did not assume that any transcription convention would directly reflect the true 'real' account of the actual interaction. I recognised that the process of recording and the process of transcribing, both structure the data in some way and that the perfect transcript is 'illusory and time-consuming' (Silverman, 2006). From a pragmatic position, I adopted a transcription process, which included a level of detail that suited the purpose of my analysis and reduced the possibility of altering the meaning of informants' accounts. For clarity non-word sounds or words and phrases that were immediately self-corrected or repeated were not included in the findings unless they indicated an intentional change in meaning

I ensured that the same methods of transcription were used across all interviews, which included a verbatim account of all verbal content (see Appendix 4). At the

same time as being aware of the value of transcribing the material myself, I accepted that due to my lack of transcription experience combined with time constraints the most feasible option was to have the interviews professionally transcribed. I nevertheless still regarded myself as having a role to play in the transcription process, since I carefully reviewed the transcription against the original audio recording correcting any errors and ensuring the meaning was consistent across audio and transcription. Also at this time, I anonymised the entire interview transcripts by removing all material that might support identification.

3.7 Data Analysis

During the analytical process, I drew on elements of both grounded theory and discourse analysis. This pluralistic approach facilitated a deeper understanding of contradictions and ambiguities within the data and stimulated and extended the way I thought about the data and to challenge any initial assumptions. Within this case study, the comparative aspect of my analysis formed an important analytical tool rather than overarching component. I used the comparative element to inform theoretical understanding of recruitment, as well as to detail important divergences and convergences across the adult and child setting. A core principle underlying the analytical process was the ongoing, iterative nature of my analysis which began during my data collection and continued throughout the writing process to the point my final draft was completed. Despite my analytical process being essentially recursive it could be broadly aligned to four recurring stages (see *Table 3.1).*

TABLE 3.1: The analytic process

Definition	Purpose	Process
Stage 1 Familiarisation	To become fully acquainted with the data and to understand its meaning in entirety (Charmaz, 2004) To identify what people are saying that is relevant to the research objective (Ritchie et al., 2014)	Reading transcripts & listening to audio files making handwritten notes on transcripts, checking ambiguities. Reading field notes and making case summaries. Identifying key ideas within individual accounts. Discussion with supervisors
Stage 2 Initial coding	A formal system to manage and organise the data (Bradley et al., 2007). To allow systematic and comprehensive coverage and comparison of the data-set (Ritchie et al., 2014) To begin to identify key experiences described/grounded in the data and to begin to uncover links between these experiences across and within accounts (Bradley et al., 2007)	Uploading of transcripts to qualitative data analysis software QSR NVivo 10. Using this software to assist in grouping of data according to descriptive codes derived from the data. Supervisor feedback and group coding of selected data Returning to stage 1 where necessary.
Stage 3 To interpret the data conceptually while remaining sensitive to the context	To identify dominant recurrent unifying ideas or concepts occurring across the data concerning the research objective (Bradley et al., 2007; Charmaz, 2006). To address hidden assumptions and taken-for granted knowledge (Holt, 2011; Burr, 2003). Examine data discursively identifying significant scripts contradictions, ambiguities and tensions (Potter & Wetherell, 1987)	Analytical memo writing of key ideas to assist in moving from descriptive to conceptual interpretation. To complete case based summaries for each informant to highlight variation within accounts. Compare and contrast coding between cases, across cases and sub-sets of data. Recode or refine dimensions of existing codes, using insights gained from analytical from memos. Supervisor feedback, continued group coding of selected data. Returning to stage 1 and 2 where necessary.
Stage 4 'Theoretical rendering.' Sensitising concepts	To actively look for meaning in the data to explain features and patterns found across the data set (Frost; Ritchie et al., 2014). To develop a central key analytical concept grounded in the data. To use theory as an interpretive device to develop my understanding of the data further (Bowen, 2006; Charmaz 2006).	Continue cross-examination of the data described in stage 1-3 Primary analytical tool active writing (Liebenberg, 2016) To examine how the literature defines fairness as a theoretic concept. To use this concept as a tool to examine my data further.

In the first instance, I kept field notes (Appendix 5) which I completed after each interview. Initial thoughts, feelings, regarding the course of the interview, how the interviews were negotiated and any significant discussions which occurred outside the recordings were included. I viewed these field notes as an important supplementary device which helped to enrich and contextualise the interpretation process (Wolfinger, 2002). In addition, once the interview had been transcribed I also wrote an initial narrative case summary (Appendix 6) related to my initial reflection on my interpretation of the content/co-construction of the interview.

My focus for the summary was to capture the main discourse and familiarise myself with each interview capturing key features of interest to the research aim, while paying attention to any inconsistencies or ambiguities. As the analysis progressed, I began to compare across different narrative summaries, which enabled me to get an idea of the main issues being raised.

A core tenet of all grounded theory and indeed much qualitative analysis which also formed another central component of my analysis involved the 'constant comparative method' first described and formalised by Glaser & Strauss (1967) (Strauss & Corbin, 1998; Charmaz, 2006). This process began once I had received several transcribed interviews, anonymised and checked for accuracy. They were then entered into the qualitative analysis software QSR NVivo Qualitative analysis software (QSR NVivo 10). During the constant comparative method, I continued to listen to the recorded interviews in conjunction with the written text throughout the analytical process, to address any ambiguity and add context and authenticity to the interpretation of the interview.

This process involved breaking the data down into meaningful components or 'codes' to facilitate the comparison of ideas within and across transcripts, to identify recurring or unifying features within the data. From a constructionist position, I did not view the analytical process as passive in which themes or concepts simply 'emerged' from the data. Rather I recognised that I, in effect, created themes or conceptual categories to help make sense of the meanings in the data and construct a comprehensive account of the 'case'. The purpose of my analysis was not to measure the prevalence of ideas or views but rather to map the range and diversity of how people made sense of recruitment and to explore and explain the links between unifying concepts identified within the data.

The way I initially grouped the data in the first instance was primarily descriptive, with the aim to keep the codes as similar to the data as possible. This coding then became more focused through continual comparison within and across individual transcripts. Writing analytical memos to record my reflection on concepts and patterns identified with the data, in combination with a recursive analytical process *(Table3.1)* facilitated this process. Also, contradictions or tensions occurring within narrative summaries alerted me to test and examine these tensions conceptually across broader patterns identified within the data. Continually returning to the individual narrative helped avoid the conceptually focused analysis becoming de-contextualised or 'disembodied'. Furthermore, the analytical process was guided by my supervisors, who co-coded a selection of transcripts and continually checked the analytical process. Sections of my findings were also presented at methodology conferences as part of the North West Hub and within the regional paediatric clinical research facility and Clinical Trials Unit, from which I received further feedback.

While my approach was principally data-driven, to avoid introducing preconceived outcomes, I nonetheless recognised the value of adopting an integrative approach to facilitate the comparative focus of my analysis. I therefore used both inductive (ground -up) and deductive (start list) organising structures to the data (Thomas, 2011; Bradley et al., 2007). The start list I initially used to structure my analysis was around an informant's role and responsibility in the recruitment context

i) The voice of adults: the autonomous individual
ii) The voice of parents of children: the family context
iv) The voice of children and teenagers: emerging autonomy
v) The voice of adult and paediatric practitioners: the recruiters

I did not treat these social roles as discrete categories but rather as a feature of the social landscape which facilitated the emergence of different patterns (Ritchie et al., 2014). Comparison across these informant groups enabled me to assess whether the same elements were more apparent or were described differently in one group than another, providing an important analytical mechanism to develop insights into how the process of recruitment was understood (Bradley et al., 2007; Stake, 1995). Data was initially coded within each sub-group to avoid forcing unifying features across these different groups and to ensure divergences were identified. The analytical process involved a continuous process up until my final conceptual framework was formed *(Table 3.2).*

TABLE 3.2: Identifying common elements: When is a research offer fair?

A rational discourse	Weighing things up Information disclosure Judgements of risk/ safety Does trial/study make sense Burden/inconvenience
A psycho- moral discourse	A progress narrative A moral/social responsibility/duty/obligation A moral education Intrinsic value pro-social/inner glow Optimism and hoping for the best Balancing hope and duty Hope as coping Hope for a cure The morality of marketing
A social discourse	Impact of relationships Comfort/social ease Value/empathy Assurance/reassurance Centrality of trust Trust and acquiescence
Factors influencing informants' views of a fair offer	
Personal circumstances	Responsibility(autonomy/dependency) Health status Past experiences Personal resources
Study design	Trial design Equipoise Randomisation Placebo Treatment Preference

During the final stages of my analysis, I moved away from the software to a period of active writing, which became my primary analytical tool (Charmaz, 2006; Liebenberg, 2016). This extended period of writing and thinking enabled me to examine ideas more closely, refining the focus my interpretation. By taking a qualitative case study approach involving multiple perspectives an extensive amount of data was generated. Analysis dealing with a vast amount of data

concerning many different viewpoints resulted in inevitable inconsistencies and intricacies. While I addressed some of these intricacies, my overarching aim was the identification of commonalities or unifying concepts' which could account for both convergences and divergence across these sub-groups, providing a cohesive account across this multiplicity. I aimed to characterise common elements which contributed to how a child, parent, adult or practitioner viewed the process of trial recruitment.

When and how I engaged with existing empirical and theoretical knowledge involved several distinct decisions. Engaging with the extant literature before undertaking my primary research was essential, to position my study within the wider literature and to support my rationale. For example, it was necessary to establish that the aims were novel and that the study would not be simply replicating a previous one. Towards the end of the analytical process, I also began to draw upon relevant themes within the literature to help interpret my findings. However, I delayed an in-depth critical engagement with the empirical qualitative recruitment literature until after the analysis of my interview data was complete. This would avoid imposing preconceptions and assumptions on to my findings and enable me to repond better to the data with original insights (Charmaz, 2008). Therefore full engagement with the extant recruitment literature took place in the discussion section, following the presentation of my findings.

I identified three patterns or common discourses centred on perceptions of 'fairness'. I chose the term fairness, as a simple term to convey how informants made sense of the process of recruitment. The term is also relevant to childhood, where many things may seem unfair and yet it remains an overarching ideal of relevance well beyond childhood. Nevertheless, rather than a universal ethical principle or ideal of fairness, relating to various types of justice, informants'

conveyed personal judgements in relation to the fairness of the offer being made and their chosen course of action. These perceptions of fairness were personally orientated and coincided with, for example, what a mother judged as fair for her family and her child, or what trial a practitioner considered to be fair for their patients. Personal perceptions of the fairness of trial related costs and the benefits of a particular trial were *'weighed up'* using a '*logical head'* in which risks were prioritised. The fairness of an offer was also constructed according to the social context in which recruitment occurred and whether informants felt comfortable and at ease during the social exchange, in which a concept of trust was pivotal. Informants also constructed the fairness of a research invitation in terms of the psychological and moral value of participating in clinical research.

Fairness was sometimes explicit and sometimes implicit in informants' talk and while it could not be applied to every aspect of my findings, the meaning and implications of fairness provided important 'theoretical rendering' and conceptual development of my findings (Charmaz, 2006; 1990). From this position, I was able to distinguish three distinct yet interdependent discourses - a rational, a social and a psycho-moral – which influenced and shaped how informants made sense of trial recruitment. These findings illustrated a labile interpretive context relating to how informants worked to construct an account of recruitment according to these three discourses which were influenced by several key mediating factors. These mediating factors included personal circumstance, health status and the particular costs-benefits and trials or study design. Within this comparative design, personal perceptions of fairness took on different forms depending on an individual's sense of responsibility, whether they were parents acting on behalf of their child, or adults acting autonomously, or children within the family context or practitioners responsible for the well-being of their patients.

The findings of this study will be presented over four related chapters. Chapter four will provide the contextual details concerning participating CF centres and individuals who participated in the study. I will then introduce the conceptual framework in more detail at the beginning of chapter five around which the subsequent three chapters will be structured. Thus chapters Five, Six and Seven will present findings which illustrate a rational, a social and a psycho-moral discourse characterised by how informants made sense of the recruitment process.

3.7 Ensuring quality

I considered quality from an interpretive position, as part of the research process, reflecting an internal set of values inherent in qualitative inquiry (Ritchie et al., 2014, Thomas, 2011a; Mason 2002). Rather than reducing it to specific criteria or checklists of techniques deemed as indicators of quality (Reynolds, 2011). I perceived myself as an active agent who, like the informants', was actively making sense of the world (Charmaz, 2004) with the interview data representing meaningful accounts of informants' perspectives and experiences of trial recruitment. I accepted that there is no final answer to questions about the extent to which "our co-created constructions are trusted to provide some purchase on some important human phenomenon" (Guba & Lincoln, 2008). However, I also recognised the value of an ethical, systematic, comprehensive, reflexive approach towards enhancing the credibility of qualitative findings, which must ultimately, be judged by the reader (Tracy, 2010; Charmaz, 2006).

This qualitative case study was developed with the input from experts in the field of trial methodology, qualitative research and cystic fibrosis. Guidance was also sought from the young person's advisory group. Interview questions were reviewed

by these groups to ensure coherence and authenticity for both informants taking part in this study and recruiters within the clinical setting. This input helped to ensure that the interviewing was 'fit for purpose'. Sampling across multiple CF centres within the UK enabled the research burden to be kept to a minimum while accessing a diversity of experience and improving the scope for wider inferences to be made about the findings. The use of field notes and a repeatedly returning to the recorded interviews, rather than just re-reading transcripts, added valuable context to the interpretive process, supporting the authenticity and coherence of the findings. Systematic scrutiny, by my supervisors of my ongoing data analysis provided critical feedback and was invaluable in refining my interpretation of the data, enabling me to broaden my focus and avoid becoming submerged in the richness of the dataset. Further interim feedback of my analysis from members of the North West Hub and practitioners within the clinical setting enabled me to clarify my ideas further while ensuring I remained focused on findings that would be most meaningful for the clinical setting.

Data analysis was based on the entire dataset, and illustrative quotes were used from across all interviews. My aim throughout this case study was to deliver a meaningful account, which adequately captured and represented the informant voice while achieving my overall research aim - to further understanding of the process of trial recruitment and contribute to practice. Within the findings chapter, I sought to provide adequate description and coverage of the data, while ensuring that interpretations were transparent. In the discussion, I further examine the findings in the light of existing evidence, so that the reader can decide the coherence and originality of my interpretations.

My work to make sense of informants' accounts is an interpretive activity. Therefore it was critical that I was continually involved in the process of self-questioning or 'reflexivity' - 'the process of reflecting critically on the self as the researcher, the 'human instrument' (Lincoln, & Guba, 2000). Thus, I continually questioned my assumptions and interpretations throughout the research process (Thomas, 2011a; Merriam, 2009; Mason, 2002). Keeping a reflexive journal facilitated this process and provided a vehicle for me to critically appraise my perspective and those of the informants, and examine how these influenced the collection and interpretation of the data (Emerson et al., 1995).

Striving to remain aware of my own and other influences provided me with valuable insights into the subject under investigation. I also endeavoured to use my personal experience of parenthood, as a person accessing the health service (both as a parent and a patient), as a former health care provider and as a health care researcher, to facilitate and focus the research so it was meaningful and relevant to other parents, individuals, practitioners and to the broader research context. This subjectivity assisted in the establishment of rapport and trust with informants - both with practitioners, to allay fears of being assessed about their recruiting abilities; and by bringing an understanding attitude towards the family dynamics and individuals living with a long-term health condition. Throughout the research process, I aimed to remain aware of the importance of finding the right balance between drawing on my experiences while staying critically aware of my own assumptions and preconceptions.

3.8 Summary

Within this chapter, I have provided a detailed account of the research process adopted for this case study. In-depth semi-structured interviews comprised the main data collection method, which was supplemented by field notes. The analysis involved an iterative process which continued up until the latter stages of my final write-up. In the next chapter, I will provide contextual details of the data that was collected for this case study.

CHAPTER 4: CONTEXT FOR STUDY FINDINGS

4.0 Introduction

The findings of this study will be presented over four interrelated chapters. This first chapter provides details of study setting, sampling and the characteristics of the participating CF centres and informants. This chapter therefore provides an essential context and detail for the reporting of the case study findings in the subsequent three chapters. I will then introduce the conceptual framework in more detail at the beginning of chapter five, around which the subsequent three chapters will be structured.

4.1 Details of research setting

My original sampling strategy was to include four regions (Region A-D, *Table 4.1*) within the UK. Each region containing an adult and a paediatric specialist CF centre.This strategy was adopted to reduce the research burden on participating centres, while maximising the variability of the sample and enabling the most efficient use of resources regarding travel and administration. As initial engagement with CF centres, in particular, adult centres, proved protracted and uncertain I decided to extend recruitment to include additional UK regions (*Region E-G Table 4.1)* to ensure an adequate sample was achieved within the time constraints of the study. This sampling of CF centres was guided by CF experts in the field, the Local Clinical Trials Research Centre (CTRC) and the managerial team of my PhD and involved inviting five paediatric CF centres and eight adult CF centres to act as Patient Identification Centres (PICs) for this study (Table 4.1). In addition, due to the initial difficulty in enrolling adult CF centres, following collaboration with the CF

expert patient advisor (EPA), a number of adult informants were invited to take part in this study through the CF Trust (Table 4.1).

TABLE 4.1 Sampling of specialist CF centres

UK Region	Paediatric centre	Adult centre
A	agreed	agreed
B(b[a)]	agreed	declined
C	agreed	agreed
D	agreed	agreed
E	agreed	declined
F	N/A	agreed
G	N/A	agreed
CF Trust	N/A	agreed
Total	5 centres	5 centres (+ CF Trust)

a - denotes shared care clinic where CF care provided by both the local hospital and the nearest specialist CF centre.

The sample comprised five paediatric specialist CF centres and five specialist adult CF centres who agreed to take part in this study *(Table 4.1)*. Out of the eight adult CF centres contacted, three declined to take part. One stated lack of resources, one implied concern about research burden. For the third centre, their reason for declining remained unclear, as the hospital research committee had approved the study and some practitioners had expressed a keen interest.

There was some variability between the ten participating CF centres with regards to the demographic areas covered, the size of the CF population and the facilities available. For example, for paediatric centres, the mean number of active patients registered with the centre at the time of data collection was 153 (range 58-293) which included shared care patients. For the adult centre, the mean number of active patients registered at the time of data collection was 264 (range 63-638). All participating centres were based in large, research active teaching hospitals in seven

UK cities. At the time of the interviews, all the participating paediatric CF centres and one adult centre were involved in the CF trial TORPEDO-CF, which was open to recruitment at that time. All sites were also either currently involved in or had recently been involved in recruiting to other CF trials or clinical research, involving both publically funded 'in-house' and commercial drug trials.

4.2 Sampling of study informants

The patient and parent sample for this study was recruited across 10 CF sites (5 child and 5 adult), using a combination of consecutive and purposive sampling to encompass diversity. Individuals were invited to consider participation in this interview study by a member of the CF team and/or researcher from the Local Clinical Research Network (LRN). Families at child centres B and C were invited by a member of the CF team which typically involved a CF nurse specialist or a CF consultant. At the remaining child centres families were approached by either a research nurse or a member of the CF clinical team (described as Recruitment point A, Table *4.2*). In contrast, in the adult setting, all potential informants were approached by a member of the CF team as no research nurses were available and CF practitioners appeared to prefer to take on this role themselves.

The sub-sample of adults recruited though the CF trust, comprised either CF Trust EPAs (who were invited to take part by the EPA supporting this study) or were individuals who responded to an advertisement on the CACE Trust website (developed with the support of the study EPA).

Practitioners were invited to participate in the study either by myself during site visits or via the Principal Investigator (PI) at each participating CF centre.

Practitioners who were interested in participating in the study contacted me via e-mail and a date and time for the interview would then be arranged. All practitioners who contacted me via e-mail agreed to take part (*Table 4.3*)

TABLE 4.2: Recruitment of patients and families

CF Centre	Child CF :	Patient families		Adult CF centre: adult patients		
	Point A: *approached by a practitioner at CF centre*	Point B: *agreed to be contacted*	Point C: *consented to interview*	Point A: *approached by practitioner at CF centre or Trust*	Point B: *agreed to be contacted*	Point C: *consented to interview*
A	14	12	8	4	1	1
B	6	5	5	N/A	N/A	N/A
C	7	6	4	7	6	6
D	14	5	3	5	4	1
E	5	4	3	N/A	N/A	N/A
F	N/A	N/A	N/A	4	4	4
G	N/A	N/A	N/A	4	3	3
CF Trust	N/A	N/A	N/A	6	5	5
Total	46	32(69)	23(50)	30	23(73)	20(67)

Data are presented as n (%)

The final data set comprised 82 informants; 20 adult patients, 23 families (22 mothers, eight fathers, and 12 children) and 20 practitioners, across five paediatric and five adult CF centres *(Table 4.2; Table 4.3).*

TABLE 4.3: Recruitment of practitioners

CF centre	Child specialty			Adult specialty		
	Point A: *approached by myself or PI*	Point B: *Received e-mail*	Point C: *Consented to interview*	Point A: *approached by myself or PI*	Point B: *Received e-mail*	Point C: *Consented to interview*
A	5	2	2	1	0	0
B	7	3	3	N/A	N/A	N/A
C	2	2	2	3	3	3
D	2	2	2	2	2	2
F	3	3	3	3	2	2
G	N/A	N/A	N/A	2	1	1
Total	19	12(63)	12(63)	11	8(72	8(72)

Data are presented as n (%)

4.3 Patient and parent sample characteristics

Within the section that follows, I give an overview of the socio-demographic, clinical and research characteristics of the patient and parent sample.

4.3.1 Socio-demographic and clinical characteristics

Most parents commented on a lack of family history or prior in-depth knowledge of CF and the '*shock*' associated with their child's diagnosis. Parents of infants described themselves as still in the process of coming to terms with their child's condition. Many spoke of how their child had been diagnosed through the newborn screening which was brought in as a standard programme in 2007 (CF Trust, 2015). The parents valued this early diagnosis while parents of older children, whose condition was often diagnosed later in childhood, appeared to find the diagnosis process more complicated and drawn out, and hence, more difficult.

A family's main concerns were related to lung complications although several spoke of the liver and digestive system being more severely affected, with one teenager requiring a referral for a possible liver transplant. Many children had undergone surgery during early childhood spending periods in hospital. Some of the children were described by parents as being lucky and not displaying many symptoms. Other families of older children spoke of their child's health as relatively stable while also describing many defined periods of ill-health and instability. Several children and parents talked about being fitted with a porta-cath (an implantable venous access device) to reduce the stress caused by repeated blood extraction or the administration of IV drugs.

The typical age of diagnosis for the adult sample was much later than the paediatric sample. Only one informant described being diagnosed at birth due to the bowel complication- meconium ileus characteristic of CF. How adult patients described their health status varied in severity, intensity and range of physiological symptoms. However, most adult patients acknowledged that their health was fluctuating and deteriorating. Many adult patients spoke of their parents being told that they may not live until adulthood. Three had siblings who had died of CF, one adult patient had a sibling living with CF, and three of the adult patients were themselves, parents. One informant was post lung transplant, one was post liver transplant, and a further adult patient was on the liver transplant waiting list. Another was on oxygen supplementation therapy[5], and several had developed CF related diabetes. At the time of the study, six individuals were currently unemployed due to a deteriorating health status, and the remaining participants were either in full or part-time employment or full-time education *(Table 4.4).*

Socio-demographic characteristics of the patients and parents who took part in this study are detailed in *Table 4.4* below. For children aged seven years and older, both the child and their parents were invited to participate in this study; otherwise only the parent was invited. Ten of the patient families had infants aged less than seven years of age, with six of these children aged <2 years (median age = 1 year; range <1-5years)

[5] The most serious complication of CF relates to respiratory insufficiency and oxygen supplementation therapy has long been a standard care for individuals with chronic lung disease associated with hypoxemia (abnormally low concentration of oxygen in the blood) (Elphick & Mallory, 2013)

TABLE 4.4 Socio-demographic characteristics of the patient/parent informants

	Child patients	Parents of child patients	Adult patients
No. of informants	12	30	20
Median age (range) years	13(8-17)	37(24-50)	29(19-63)
Gender			
Male	5 (42)	8 (27) [b]	11(55)
Female	7(58)	22(73)	9(45)
Ethnic group [b]			
White	N/A	28 (97)	19(95)
Asian or Asian British		1 (3)	1(5)
Employment status	N/A		
Full-time		12 (40)	7(35)
Part-time		9(30)	5(25)
Not employed		8 (27)	6(30)
Further education		1(3)	2 (10)

a - Ethnic group data was classified according to those recommended by the 2001 census in England and Wales developed by the Office for National Statistics (ONS,2001)
b - Data are presented as n (%) unless otherwise stated

During my analysis, I decided to exchange my original numerical coding system for pseudonyms for all 'patient' informants. This was prompted by the comments made by informants during interviews, about the importance of being treated as '*a person rather than a number'* in the context of research. For clarity parent informants were referred to as mother or father of the child rather than being given a pseudonym of their own e.g. Mother (Alice 3y).

4.3.2 Research experience

With regards to the clinical experience discussed in the interviews, I defined any direct approach or invitation about clinical research to an eligible family or adult patient as 'research experience' regardless of whether the child or adult enrolled or participated in the trial or study. The extent to which informants differentiated clinical trials from other types of clinical research was variable and dependent on experience and knowledge. Consequently, many informants referred to clinical trials as 'studies' and indeed some patient information leaflets defined a clinical trial

as a 'research study'. For clarity throughout my findings I refer to research that does not involve a clinical trial as a clinical study.

Informants' clinical research experiences were variable. However, due to the nature of CF and the significance of maintaining lung health, much of the research described by informants focused on treatments for improving or maintaining lung function *(Table 4.5)*. Therefore, many patients and families described being approached about nebulised drug trials intended to improve or preserve lung function or antibiotic drug trials designed to treat respiratory infections. In the main, for parents of infants and younger children, their research experience consisted of an invitation to participate in a current antibiotic trial, TORPEDO-CF.

TABLE 4.5: Research experience

Research experience	Child (no. of approaches)	Adult (no of approaches)
Current/ongoing		
Clinical trials		
Antibiotic trial (TORPEDO-CF trial)	10	1
Nebulised drug trial	3	0
Novel drug trials	0	2
Clinical studies	0	2
Previous two years		
Clinical trials		
Antibiotic trial	0	1
Nebulised drug trial	3	6
Novel drug trials	1	3
Other trials	2	3
Clinical studies	5	11

The TORPEDO trial compared two types of eradication therapy to treat a lung infection-pseudomonas infection (*Pseudomonas aeruginosa)* and involved randomisation to either 14 days of intravenous antibiotic therapy or 3 months of

oral antibiotic therapy. *Pseudomonas aeruginosa* is a commonly occurring bacterium infecting 80% of people with CF by age 18. The infection is linked with a more rapid decline in lung function and is a significant predictor of mortality (Balfour-Lynn, 2008). Six informants described being approached about trials of new drugs involving gene therapy or mutation specific therapies aimed at correcting underlying cellular dysfunction linked to CF. Informants also described being approached about clinical trials which did not involve lung focused medicinal products, including trials aimed at treatment and prevention of drug related osteoporosis, physiotherapy trials and nebuliser 'device' trials. Many informants, particularly adults described other clinical research experience which included observational studies involving kidney function, glucose monitoring, viral monitoring, nasal tests, mental health questionnaires, and sleep and dietary monitoring.

In the first instance during interviews, I tended to begin each interview by exploring the most recent trial and research experiences, and from here informants chose to pursue issues they felt were most relevant. As noted above within Table *4.5* I have detailed informants' most recent research experiences, within the two years preceding their interviews. However, some informants chose to talk about earlier experiences of research; particularly ones they felt had been especially salient. Where these were informative, I have included them in the analysis. Several patients and families (n=5) had no direct research experience, and their views on clinical research were used to supplement issues raised by those with direct experience.

Of families with children, 75% reported having been approached to take part in a clinical trial on at least one occasion. Furthermore, 39% described being invited to take part in a clinical trial on more than one occasion, and 87% of families indicated

they had been approached about clinical research while attending a paediatric CF centre. Of the adult patients, 75% reported having been approached to take part in a clinical trial on at least one occasion, and 55% indicated they had been approached on more than one occasion. With regards to clinical research in general, 90% of the adult patients reported having been invited to take part in clinical research. Moreover, several adult patients indicated that they had been approached on numerous occasions about clinical research including clinical trials, but they did not remember the details of many earlier studies as the approach had typically occurred some time ago.

4.4 Practitioner sample characteristics

Many of the practitioners (60%) interviewed were specialist respiratory consultants or registrars (60%) (*Table 4.6).*

TABLE 4.6: Characteristics of practitioner sample

	Paediatric specialty	**Adult specialty**
No. of practitioners	12	8
Gender		
Male	7	3
Female	5	5
Professional status		
Consultant	5	3
Registrar	3	1
Allied Health Profession (AHP)	-	1
CF Nurse Specialist	2	3
Research Nurse	2	-
Length of practice, years		
<10	-	1
>10	2	-
>15	2	2
>20	5	5
>30	2	-
>40	1	-

The remaining practitioners included specialist CF and research nurses and one allied health professional (AHP). Eight of the practitioners worked solely in the sub-specialty of CF, and the remaining practitioners worked in respiratory or general medicine, which incorporated the sub-specialty of CF. Practitioners had levels of experience ranging from six to over forty years of experience since qualifying, with most (74%) having over 15 years of experience.

For clarity and to preserve anonymity I referred to practitioners who agreed to participate by their generic job title such as nurse or doctor combined with a unique identification number e.g. Nurse 1. As the majority of doctors in the sample were male (n=10), I decided to refer to all doctors using the masculine gender, to protect the anonymity of the participating female doctors. Practitioners' research experience was varied although all had experience of approaching patients about clinical trials and all but one practitioner had direct experience of approaching patients with CF about clinical research.

4.5 Details on interview data

The child sample resulted in 31 interviews (19 parent interviews; 9 child interviews, three family interviews) producing over 28 hours of audio- recorded dialogue. Three interviews were conducted in the hospital while the patient was an inpatient and the remaining interviews (n=28) were carried out at the informant's home. As indicated above, where children were aged seven years and over both parents the child and were invited to take part in the study. For eight families both the child's mother and father agreed to take part in the study, and in each case, these parents opted for a joint interview. Of the children who chose to be interviewed three children chose to have a joint interview with their parents. The remaining children

were interviewed separately although their parents were present for at least part of the interview and on most occasions parents contributed to some degree. Parents of younger informants remained present throughout the interview. One teenager declined to be interviewed, although his parent took part in an interview, and the parents of another teenager declined to be interviewed. The length of parents' and joint family interviews ranged from 26 minutes to 113 minutes; the mean duration was 66 minutes. Children's interviews ranged from 10 minutes to 38 minutes; the mean duration was 26 minutes.

Twenty adult patients were interviewed producing over 22 hours of audio-recorded dialogue. Within the adult sample, only the patient themselves took part in an interview, although other family members were occasionally present at the informants' request. Two adult patients were interviewed at the CF centre, 17 were interviewed in their homes, and one was interviewed at another place of the informants' choosing. Adult patient interviews ranged from 28 to 116 minutes; the mean duration was 67 minutes.

I interviewed twenty practitioners, 12 based in a child setting and eight within an adult setting, producing over 22 hours of audio-recorded dialogue. All practitioner interviews took place at the hospital in which they worked. Practitioner interviews ranged from 40-92 minutes; the mean duration was 67 minutes.

4.6 Summary

This chapter has detailed the contextual information for this study sample upon which the next three findings chapters are based. Within the subsequent three chapters, the substantive findings in relation to informants' views and experiences of trial recruitment will be presented.

CHAPTER 5: FINDINGS
WHEN IS A RESEARCH OFFER FAIR? - A RATIONAL DISCOURSE

5.0 Introduction

This case study of how informants made sense of research invitations illustrated an intricate and diverse picture involving many inter-related factors. In responding to this richness of the data, this analysis sought to identify key concepts that could explain divergences and convergences across informants' experiences and expectations, providing a broader description and understanding of the process of trial recruitment. My analysis indicates that informants were able to negotiate the uncertainty inherent in clinical trials, in terms of personal perceptions of fairness that centred around three prominent discourses, a rational, social and psycho-ethical discourse.

Even though the three discourses were typically interwoven and interdependent within accounts, for the purpose of analysis, I have aimed to present each discourse separately. Therefore, analysis of the data within the framework of these three discourses is presented in this and the following chapters. Within this first chapter, I examine the data from the view of a rational discourse. I examine informants' accounts of how they rationalised the choice they faced and their actions and the extent to which their accounts corresponded with normative assumptions of decision-making. I will also examine to what extent medico-legal requirements of informed consent contributed to their view of a fair research offer.

5.1 A rational discourse: Weighing things up

A central feature of this rational discourse was informants' construction of a process in terms of balancing factors that typically corresponded with their perceptions of the costs and benefits of participating in a particular trial or study. Consistent with normative models of decision-making, patients and parents spoke of a process of '*weighing up of options'* or a '*weighing up of pros and cons*' to '*try and do what is best'*.

> *I suppose you always worry you don't know whether you're doing the right thing or not, you just, you know you've got to I suppose weigh up the options and try and do what's best, and then you've just got to get on with it really, yes*. Mother (Dylan 2y)

> *Looking at the pros and cons, would it have any effect on her health, detrimental effect, so making sure that it's not going to do her more harm than good I think was a massive decision[...]* Mother (Rachael 10y)

Megan had been invited to take part in various clinical trials on numerous occasions, some of which she had agreed to and others she had declined. Her quote below captures the predominant features of the 'weighing up process' Megan engaged in, which characterised this rational discourse.

> *If they wanted me to come back say twice a week for a blood test often I would just say I am really sorry no because I am here a lot already and it's quite a long way away, and I don't want to commit that amount of time especially if you are feeling unwell and quite tired it's just, you think I can't really do that. The second thing is how invasive the trial is so if it's just part of your clinical routine they want to take an extra vial of blood or get you to do an extra test it's not too bad but if they want you to start having overnight stays in hospital or more invasive things that are*

painful as well that used to kind of influence me if I wasn't really feeling up to that, I would say no to that. And then finally often if I thought oh this sounds like it could be a good new treatment or this sounds actually like it could be really beneficial then I would think I want to give my time to that so that this can come to fruition so those are the three main things that kind of would go through my head when being approached for a trial . Megan (26y)

Within the accounts of very young informants, a 'weighing-up process' was either less evident or not present. However, some child informants, in particular teenagers, did describe a weighing-up process comparable to that of adults' and parents' accounts. For example, *Rachael's* account illustrates which factors she considered before agreeing to participate in an on-going clinical trial involving a nebulised drug.

Important was should I do it because of the needles, but I have had so many I thought should I do it because maybe I might enjoy it, or should I do it maybe because should I try a new inhaler, maybe it might be nasty, but I ended up doing it because they said to me. Afterwards, he said you can do it because they are thinking it might… because we take bloods, it might help you because you have bloods at the start and then afterwards, to see if it could help every CF[…] Rachael (10y)

Rachael considered the possible invasiveness of the trial relative to the invasiveness of her routine treatments. Furthermore, her acceptance that the inhaled drug '*might be nasty'* indicated an awareness of potential risks and side-effects. Her account also indicated awareness of personal benefits, in that she considered whether she '*might enjoy'* the experience. Consistent with many of her adult counterparts, Rachael's assessment of direct costs and benefits were influenced by her personal disposition towards the generalised aims of clinical research.

Despite many accounts of the weighing process being variable and personally orientated and often extending beyond standard tangible trial costs and benefits, an informant's endeavour to rationalise their actions was a predominant feature. Whether informants described making a '*snap decision'* or a period of prolonged deliberation, they emphasised how they had engaged in a rational process of '*weighing up the pros and cons'* in which they used their *'logical head'* to reach a reasonable decision. In this respect, their discourse mirrored a particular normative model of decision-making which assumes people are 'rational' and deliberative in how they approach decisions**.**

5.2 The weighing up process: autonomy, responsibility and dependency

The characteristics of the weighing -up process were broadly comparable for adult, parent and some child informants, each group portraying a careful balancing of issues relating to perceptions of benefits and burdens. Nonetheless, noticeable divergences were also evident across the groups.

5.2.1 Autonomy: 'is it worth the risk'

An adult's capacity to act autonomously within the research context was conveyed as involving both expectation and responsibility. Many individuals had been approached about clinical research on numerous occasions; and their accounts illustrated how they had become accustomed to deciding for themselves what treatments to accept or decline based on their personal clinical and research experiences. Consequently, for many adults, decision-making in the context of research was frequently perceived as relatively 'straightforward' compared to decisions they have had to make in the clinical context. For Instance, John who had undergone transplant surgery, described decisions he had had to make with regards

to trial participation, *'considering what I've been through, easy, easy, a drop in the ocean really'.*

Nevertheless, most informants recognised how the ease of the decision-making process changed with the varying cost-benefit trade-offs of different trials.

> *I think it varies from study to study like some things are really easy decisions so when you are an in-patient, I remember sometimes when they are testing what the best combination of drugs to give to you, so some people will be on 3 times a day, and some people will be on twice a day, and it's like well if I can go on them twice a day then yes, why I would be silly not to as long as you don't think that it's going to affect my health[...]* Kate (28y)

Safer more straightforward later phase trials were viewed as easier decisions compared to potentially riskier early phase trials involving higher stakes, which were typically perceived as more difficult decisions.

Unlike children and parents, adults emphasised '*where you are with your stage of health'* as a central feature in their weighing up of whether the trial was '*worth the risk'*. Comments indicated that diminishing health often resulted in heightened concerns about potential risks because they felt they, '*haven't got that spare to play with, so to speak'.* For individuals who viewed themselves as having unstable or problematic health status at the time of a trial invitation, this factor was most influential in their decision to decline. Helen, who had taken part in several clinical studies, commented that due to her deteriorating physical health and the intensity of her treatment regime, she would only consider participating in a trial if it involved a potential '*miracle drug'* that offered high hopes.

Unless all of a sudden it's going to be a miracle drug and I'm going to feel wonderful, I would never sign up because I just think back to that thinking, how much time is it going to take? You know, the impact on my life generally, you know, the extra needles, you know the inconvenience of things like that, but at that age, no not really a problem, because I was quite okay and fine, and it was almost a novelty, really. Helen (34y)

Helen reflected on how research participation during a period of relatively stable health was '*almost a novelty*' and something she could cope with. Nonetheless, she also recalled the burden and '*inconvenience*', something all the more burdensome from a position of more fragile health.

5.2.2 Responsibility: 'wanting what's best'

A parent's role in the research context was viewed as the responsibility to act in their child's '*best interests*' and do the '*right thing*'.

She is my child, and I am going to do what is best for Lily [...] Mother (Lily <1y)

I think when it comes down to your child, no matter who it is, you have this inbuilt I'm going to protect my child; I'm going to do what's right for her no matter what [...] Mother (Emily 9y)

We, me and her dad just want to do what's best for her, and if the research is going to help at the end of the day to help keep her healthy for as long as possible then, then we are happy to do whatever we can to help her. Mother (Zoe 1y)

Parents perceived that '*there is a lot more responsibility because it's somebody else's health*', and spoke of '*feeling under a lot more pressure*'. Parents positioned this *'inbuilt'*

drive to '*do what's best'* for their child's health, viewing it as part and parcel of their role of parent. They presented the everyday task '*to care for your children'* as '*a lot of pressure'* but also emphasised that this was heightened within the context of caring for a child with CF, where both day-to-day and clinical decisions were viewed as having the potential to shorten a child's life.

> *You are under a lot of pressure anyway to care for your children, but having to make decisions which could really shorten her life, because when you are talking about chest infections and things, it can affect their life expectancy [...] Even decisions like should I take her swimming because she has got a bit of a cough [....] it is still a decision you have got to make which could impact on her health […]*
> Mother (Alice 3y)

Accordingly some parents positioned their responsibility in the research context as comparable to their role in other contexts; nonetheless, some viewed this task as distinct from other types of parental responsibility and a task which they regarded as '*a lot of weight on your shoulders'*.

Nathan's mother described in detail the emotional strain she experienced in deciding on behalf of her son to participate in a trial which she believed had had a potentially serious side-effect – a cost which she countered through her belief in the value of the trial, research *per se* and her trust in the CF team.

> *The first trial which he did, was the tobramycin, his antibiotic once a day, they were giving it 3 times a day and they wanted to know whether just giving it once a day would make much difference [...] but it was a bit scary, because it can cause deafness, if it's at such a high level of, in the blood [...] it was in the back of my mind worrying about side effects and things like that. But then after thinking you know going along*

the lines again if nobody does anything, nothing will change, and treatment will always be the same, and nothing will get advanced. Mother (Nathan 16y)

This responsibility seemed to weigh particularly heavily on parents when they felt their child was too young to voice their own perspective. Parents saw it as '*something that plays on your mind'*, anticipating feelings of '*blame'* should the decision they made result in a negative outcome.

It's living with the guilt if anything does happen, isn't it? Father (Joseph 5y)

As a parent making the decision on a trial, and whether to take part or not, obviously I think you worry, you know you have reservations, and you worry. You do worry if maybe by doing it are you causing any harm [...] Mother (Dylan 2y)

In leaving parents feeling personally and directly accountable for their child's outcome in the trial, the goal of ensuring the decision about the trial was '*what's best'* appeared more burdensome. Moreover, some parents of infants less than a year old, who had either declined a trial or had not yet been approached, displayed considerable reluctance and discomfort about acting on behalf of their child while they were *'still little'.* It was notable that these parents were comparatively less favourably inclined to medical research, their descriptions of clinical trials including terms such as 'a *gamble'* or a '*lottery*' or '*being used like a guinea pig'.* They also viewed themselves as being in a period of adjustment with regard to their child's diagnosis and, for first-time parents, parenthood.

If I am honest I would probably not want Lily to do it while she was so young, only because Lily hasn't got her own say, and we are still new at it, do you know what I

mean. I suppose because any test there is a chance it could have a side effect [...] Father (Lily <1y)

These parents anticipated that with increasing age, their child would take a share of the decision making responsibility and therefore reduce the psychological unease related to this role. One parent reflected on '*the pressure being taken off her'* - a sentiment echoed by other parents - as her son became more involved, describing a sense of relief when her son reached the legal milestone of 16. This parent contrasted the '*hard' 'scary' 'frightening' 'difficult '* decision to allow her son to participate in a trial with potentially high risks when he was younger, with the '*easy'* decisions she had been involved in more recently, concerning lower risk nebuliser trials, for which her son had taken the lead role.

In the main, parents indicated that from the point they viewed their child as having their own '*wishes'*, they negotiated the nature of the child's input, while ensuring they upheld their personal and parental expectations of the '*right decision'*.

Overall you try and do what's [best] you know your child has her wishes, and you want to respect those because I want her to feel that she does have an input, but at the end of the day the responsibility was with me to actually make the right decision for her [...] Mother (Emily 9y)

How parents negotiated a child's '*wishes*' was in part determined by how they negotiated their child's involvement in other areas of their life - what one parent described as your '*family-set up.'* Existing family dynamics were instrumental in shaping broad patterns of involvement, particularly for children who were not yet teenagers. In these families, parents engaged in considerable work to pre-select

information and terms of the negotiation according to existing family dynamics, the age and developmental stage of their child and their perceived value of the trial.

> *I think it's your family setup as well because some mums I know are very controlling even if the child is like Ellie's age 14, I do know of some mums that the child doesn't go out, doesn't have many friends and just goes everywhere with mum.*
> Mother Ellie (14y)

> *I suppose it's what kind of house you grow up in and what rules you have.*
> Mother (Daniel 11Y)

Despite some parents expressing unease and discomfort in this role, many parents accepted this responsibility as a natural extension of their parental role and most parents had agreed to allow their child to participate in a clinical trial or study.

5.2.3 Dependency: I can decide but my parents' know best

Consistent with parents' accounts, how children negotiated their involvement in trial discussions was influenced primarily by their own family's model for managing roles and responsibilities. Moreover, the influence of a child's family set-up on the nature of her/his involvement in the research context was inextricably linked to their developmental stage, personal experiences of research and existing level of involvement in the clinical context.

At times children's reasoning, particularly in teenagers, appeared qualitatively similar to adults.

For instance, Clare's account below is more consistent with other adults' accounts (as opposed to parents), in that she framed the decision around the practical aspects of the trial. Parents, in contrast, were more inclined to view the decision in terms of whether it was in their child's best interests or the right thing to do.

> *I was just worried about whether it was actually going to work or not and I just thought well if I come out of it at the end and find that it hasn't worked I will feel a bit like Oh well that was a bit pointless. I didn't really want to feel like the whole thing was just a waste of time. Which I still feel the same way, really I don't, I wouldn't want to do it if I thought that it was just going to be a waste of time for a drug that doesn't really do anything*. Clare (17y)

However, significant to many children's' accounts, especially children who had not reached their teenage years, was an implicit reliance and trust in their parents' direction. While most of these children described being involved in trial discussions and some viewed the decision as being theirs to make, their accounts often indicated that their parents had engaged in the weighing up process on their behalf.

In contrast one informant chose to emphasise the carefree indifference of a *'not bothered'* teenager.

> *My initial thoughts were yes, a day off college, I didn't think… oh yes, find out how well my kidneys are doing, no it was more all right then, a day off college, not bad.* Kirsty (16y)

This teenager viewed her decision as something she made '*straightaway'*. However, despite her primary motive being '*a day off*' Kirsty nonetheless juxtaposed this with

an awareness of the objectives of the study and a potential personal benefit of participating. Furthermore dispersed throughout her narrative, akin to those within adult and parent accounts, were conceptions of costs and benefits. Though her account alternated between that of a '*not bothered'* teenager and an autonomous decision-maker, Kristy chose to place emphasis on the discourse of a *'not bothered'* teenager, perhaps as preferable to that of a teenager that has to manage a serious lifelong condition.

All children expressed awareness that trial or study participation involved making a choice and that they didn't have to take part. No child indicated they felt under any pressure from either practitioners or their parents and all but the youngest positioned themselves as having an active share in the decision-making. This finding was corroborated further by all parents acknowledging their child *'has to have a choice whether he wants to take part or not'*. However, some younger children indicated that they would feel comfortable accepting the decision their parents advocated, whether this was to say yes or no. Moreover, children's references to a weighing-up process were much less apparent. One plausible interpretation is that the shared decision-making responsibility typically described in child and parent accounts lessened the choice burden and pressure for these young people. While parents ensured they were included and had a share in the decision-making process, they took the ultimate responsibility of balancing the costs and burdens and the authority to consent or decline from their shoulders. Most child informants illustrated some awareness of conceptions of cost and benefits, albeit at times varying in focus from their parents, indicating that they did engage in a form of shared decision-making.

5.3 Information disclosure

In this section, I will examine to what extent the formal trial information featured in informants' accounts of the weighing up process. In the first section I examine how trial information figured in patients and parents view of a fair research offer. I then examine practitioners' experiences of disclosing trial related information to potential 'participants'.

5.3.1 Patients' and parents' perspectives

All except the youngest informants spoke of being given explanation and written details about the trial or study they had been invited to consider. For the most part parents and adult informants spoke about the content of the formal study information in quite generalised ways as *'fine'*, '*self-explanatory'* and *'really good'*, the *'right level'*, *'it told you everything you needed to know'*.

Some informants made a distinction between the trial related information aimed at ensuring you *'understand what the trial is about '* and then all '*the boring information '*, *'your kind of standard stuff'* that has to be included *'due to certain rules and regulations'*. For some parents, the *'legalities'* and *'legal jargon'* in the leaflet *were 'rather a strain to read'*, and *'unnerving'* and something which *'maybe could be put aside until later'*. In fact, several informants suggested they were only interested in reading the *'basic information'* concerning what the trial involved and why it was being done; and were not interested in going into all the written details. In contrast, others spoke of needing to know the trial information *'inside out'* before making a decision.

Informants viewed verbal and written information '*both together'* as necessary in deciding their course of action; however many emphasised the value of the trial

discussion. Several adults, particularly those who were more reserved about trial participation, stressed the importance of being introduced to the trial outline verbally initially, rather than being *'just handed a leaflet'*.

> *I think certainly you are going to be more engaged if it's verbal, on a one-to-one than if you are just handed a leaflet told to go away and read it, a lot of people probably stuff it down the side of the chair to be fair but, I think certainly if they can, if they can talk to you about it, and you can ask questions at the time, then it's, it's a lot more engaging.* Phil (35y)

However, informants who had consented to trials valued the written trial information as a necessary '*point of reference'* to ensure they were clear about all the stages and details of the trial.

> *That's the point where if you think oh I haven't understood that properly you can go back to it, and you can refer to it as you go through the trial and I suppose if anything crops up in the trial that you didn't read in the leaflet you have then got the leaflet to say well you didn't say this in the leaflet, so it is good to have that point of reference for yourself.* Megan (26y)

Most children recounted receiving a separate leaflet to their parents. However, in the main they did not comment specifically on the quality or nature of the written information, but rather whether they had read it or not. Consistent with many of the child informants, Clare described being given a trial information leaflet but viewed her discussions with her parents as being the more influential on her decision to participate. While children did not regard the written information as central to their decision, older children, like their adult counterparts, seemed to expect to receive

such information. Younger informants too sometimes spoke of value they attached to having received a leaflet.

All informants viewed a combination of verbal and written information as an integral component to establishing when they perceived an offer to be fair and one, they were comfortable accepting. However, there was no case in which an informant based their decision solely on assessments of the written trial information. Moreover, there was some variability as to what extent deliberation of written trial information influenced actual decisions. Francis, who had been approached to take part in two clinical trials, one ongoing, and various clinical studies, all of which he had consented to, at times conveyed his decision-making as centred on the provision and assessment of *'accurate'* information

> *I just read the blurb and sort of see if anything leaps out at me […] So long as the information is as accurate as it can be and you feel that they've presented the pros and cons fairly and you can assess it.* Francis (63y)

Francis indicated that the decisions he had made so far had largely been '*snap decisions'*. Though this might appear inconsistent with his earlier more rational account, Francis spoke about his personal disposition to clinical research and '*subconscious*' assurance about the value and integrity of the research introduced in a familiar context. This viewpoint seems to represent a more intuitive decision-making process, a sentiment which was echoed in other accounts. Many informants attributed their motivation to take part as due more to the endorsement provided by a known trusted practitioner than to any written trial information. Furthermore, some informants indicated how they viewed their decision as being made in advance of receiving all the details about the trial.

> *They give you the information to take home and read, but I would make the decision unless it was harmful, other than it being harmful for Peter, I would never, I would say yes straight away.* Mother (Peter 12y)

Consistent with parent and adult accounts, children sometimes indicated they had made their decision before reading or receiving the information leaflet, and some stated that they '*didn't bother reading*' the information leaflet at all.

However, children who didn't read the information leaflet but who agreed to take part in the trial were aware that their parents had vetted the information on their behalf.

Conversely, some informants spoke of their decision to decline as being made almost straight away before they had received all the information regarding the trial.

> *It was just such an instant decision, they would have given her longer to think about it, but she just didn't need it because she, there was no way she was not going to have IVs.* Mother (Amy 16y)

> *I think Emily and we had kind of made our mind up that if there was any chance not to go for IV and the stay in hospital […] If there was any way that we could avoid that really because she had a lot of time off school during the trial, over four months last year, and we felt personally that if Emily really didn't want to have the IV […]* Mother Emily (9y)

Each of the parents above referred to a treatment preference as the primary justification for their immediate decision to decline the trial they had been

approached to take part in, which in each of these instances involved the TORPEDO-CF trial.

One family who declined before engaging with the trial information appeared confused about the TORPEDO-CF design and they spoke of being *'scared'* and *'stunned'* about their daughter's diagnosis of pseudomonas.

> *I can't remember which way round it was, you've got the antibiotics first and then something else after and then the other one is the blowing and the antibiotics later […]* Mother (Mia 8y)

In some cases, informants implied they had made the decision to take part in research long before the trial had been offered to them. These parents did not dismiss the importance of pragmatic considerations in their decisions. However, their accounts suggested these were something of a formality, compared to how they viewed the influence of their values and beliefs. While they spoke of checking through the information to satisfy themselves that the trial would not be detrimental to their child and that it made sense, ultimately they felt they had already taken the decision.

> *When cystic fibrosis was first diagnosed in October 2010 when the baby was born, at the time we heard about cystic fibrosis, from that point, I decided to help with the research because I know that my daughter has it so I would be going through that feeling how other parents feel when their daughter, when their child has got this kind of a disease. So I decided okay, I will do kind of charity; I will try to participate in any, help or anything that can support the cystic fibrosis research.*
> Father (Anna 1y)

I've always said that I think research is a good thing and we've always discussed it and said if we were ever approached, we, you know, if it could mean a difference to Dylan's life or even Adams [Dylan's brother] *then we would more than likely say yes, so I think in a way we kind of knew anyway[...]because we'd had those conversations before it made it a lot easier for us to decide, so that made it a lot easier [...]* Mother (Dylan 2y)

5.3.2 Practitioners' perspectives

Practitioners' accounts illustrated how they had adapted their approach to information disclosure according to research regulation and their personal experience, so as to achieve what they perceived to be an '*unbiased*' presentation of the facts. Some stressed the need to *'stick to the book'* or '*remain neutral'*. One practitioner emphasised the need to balance information regarding tone and content, remaining neutral but positive, while ensuring adherence to necessary legal and ethical requirements without causing any undue concern. Others similarly highlighted the delicate balance between the importance of being frank with patients while remaining within the limits of what they *'can take'*.

It's good, to be frank with parents and tell them, rather than trying to, I mean normally we don't try to keep information from them, but it all depends on the individual parents how much they can take, because some parents can pick up on certain words and then that sort of stays in their mind all along and it will affect the whole picture Doctor 11 (child)

One practitioner whose role was purely research based was the only one to emphasise the legal and procedural requirements of the research discussion by indicating her use of the formal trial regulation guidelines (ICH (E6) Guidelines for Good Clinical Practice, 1996) as the framework for her research discussion. She

described how she would always read the information sheet to prospective families and work through the '*20 rules of consent'*. In contrast, other practitioners, while recognising the need to cover '*important points'* necessary to conform to the ethical and legal requirements of informed consent, emphasised the significance of tailoring information in a way that was the most meaningful for each individual or family. These practitioners implied that what might be perceived as '*dumbing down'* to an individual who '*wants every last detail about how many rats got the treatment before they did'* might look '*like a court order'* or '*intellectual jargon'* to another. Their accounts conveyed a sense of the delicate balance required to uphold the ethical and legal requirements of informed consent while ensuring information is tailored, so individuals do not feel overwhelmed or deterred.

Within the context of existing clinical relationships practitioners remarked on the tendency for patients to '*rely'* on '*what you are telling them'* rather that examining the trial information in detail.

> *I think they rely on what you are telling them to do. Some of them will read everything you know even the small print, but I think the majority, will you tell me about it. Well take this away and read it at home and you think you are not going to read it at home.* Nurse 1(child)

> *I'm not going to read that, is a common comment. 'I trust you', I say no, no, you're supposed to read it, 'I trust you'. The big commercial ones are the worst, American companies. So there can be pages and pages and pages, and the parents just throw that straight in the bin. [...] You tell them what it's about and say you can take this away with you and read it and if they choose to throw it away, that's their choice, but they expect us to summarise it.* Doctor 3 (child)

Practitioners described how some patients displayed a reluctance to read the trial information leaflets, particularly the denser documentation typical of commercial trials, instead expecting a trusted practitioner to summarise key points.

5.4 Perspectives on the gold standard

Within this section I will examine informants' views on the highly structured design which characterises a conventional randomised controlled trial or related trial designs (Kerr et al., 2006; Jadad 1998).As in the previous section I will examine the patients' and parents perspectives first, followed by those of practitioners.

5.4.1 Patients' and parents' perspectives

Informants varied in the detail and emphasis they gave to trial design and the process of randomisation. However, in the main, they viewed this design aspect as '*fair enough'*. Informants with less familiarity with the procedure described '*accepting it as part of the trial'.* Those with more familiarity indicated that it was a necessary feature of the trial design to enable comparison of treatments to produce meaningful results.

> *That is how things have got to be done, because… you can't pick certain people for things because that's not what trials are about, it's to see how everybody reacts to different things.* Mother (Isabel 2yr)

> *To me it's very simple we are doing a trial to see if this drug works, the only way we can do it is some of you will have it, some of you won't, you won't know.*
> Gareth (40y)

Some recognised the scientific value of randomisation as necessary for producing *'a true reflection'* of efficacy.

> *If you want to prove something is statistically significant then you have to have a way of doing it, you have to like, you have to have a control [...]* Alex (29y)

The detail and emphasis children gave with regard to the trial design was variable, according to experience and developmental level. Older teenagers who had direct trial experience were aware of the need for and the nature of randomisation and placebo, and their accounts were indistinguishable from adults and parents. Younger children with direct trial experience had some awareness of design aspects of a clinical trial, but their accounts varied in detail.

> *Well, my mum has told me that there's some real ones and some fake ones, but they're asking everyone if they know which if there are any differences since they've had it.* Daniel (11y)

> *Say someone has an infection, and the doctors never knew what it was, they would have like trials, to see if it's in anybody else.* Peter (12yr)

Some informants, while accepting the procedure, also expressed some ambivalence about the reality of accepting uncertainty and lack of choice for themselves or their child. One teenage informant understood and accepted that randomisation was part of the *'whole point of the trial'* but nevertheless described how the experience felt *'a bit weird'* in reality.

> *Obviously, it's ok that it's chosen at random it's better that way, but I still thought it was odd you know to think that someone else if I didn't get the drug, then someone*

else might, or I might get it and someone else, wouldn't. I thought that was a bit weird. Clare (17y)

Several parents' perceptions of randomisation were complicated by comments made by the recruiting practitioners post-randomisation. In the context of the TORPEDO-CF trial, Dylan's mother had struggled to balance equipoise on the part of the clinician with her motivation to do '*what is best'* for her son. She described how she would have been guided by the consultant, but because he wouldn't tell her what was best and chose to talk most about the trial, she interpreted this as an indication she should opt for it.

I would have gone on the information of the doctor, what he thought was best, but because he wouldn't tell us, because obviously, I think he was obviously trying to get us to opt for the trial, so he wouldn't give us a clear indication of what he thought was best and what everyone else thought was best [...]he was trying to kind of push us into going into the trial, not in a forceful way but that's where his information was leading, you know and that's kind of what he talked about most. Mother (Dylan 2y)

However, this parent's ambivalence in relation to the issue of equipoise and randomisation appeared to have been confounded by comments her clinician made once her son had been randomised to a treatment arm.

After they did the randomisation and it came up with two weeks of IV's in hospital, the doctor said, I'm glad that's what I would've chosen myself. So then I was a little bit worried because then I thought, well if we had home treatment, you know, it wouldn't have been getting the best, but then in the long term obviously you know the research is important[...] Mother (Dylan 2y)

Several other parents described similar comments being made by clinicians following randomisation. It is conceivable that these practitioners' comments were aimed at helping to reduce any choice conflict or ambivalence in relation to the issue of equipoise. Conversely, these comments appear to have had a counterproductive effect, leading to more '*concerns'* and potentially impairing informants' belief in the integrity of the research.

Some informants who had previously declined participation or had not yet been approached about a clinical trial remained ambivalent or concerned about the fairness of the randomisation process. These informants, while recognising the necessity for randomisation, indicated a preference for the *'newer drug'*, viewing the situation as '*a hard one'* to reconcile. Mia, who had declined several clinical trials she had been offered, captured this tension within her account. Her reflection on randomisation design illustrated the tenets of a 'patient preference trial', a design advocated by some trialists.

> *I suppose it's the only fair way to do it, but, then again, I do think in these things, that there would be a group of people who would prefer one, prefer the other and then there would be some in the middle, who wouldn't really be that bothered, that they'd do either. So I think in some ways it would be nice if there was an option, you might be more inclined to take part if you got the option that you wanted.*
>
> Mia (25y)

Another adult informant, Sara, who had declined two clinical trials, after reading a short vignette describing RCT (Appendix 7), reflected on the question of study design.

> *So it would be a group of people in group A trying that drug and group B. I think well everyone's body works differently, so the people, the treatment that is group A doesn't work, it might work with group B and vice versa. So if anything, if I was to do that, I'd try A treatment for so long and see if there's any difference and then go on to B and see if there's any difference, if anything. I wouldn't mind trying it, yes. But again if there's no side effects I probably would try it, but there's no guarantee. But again I'd like to try the two things because something that might not work with someone else might work with me [...]* Sara (30y)

Despite Sara's lack of familiarity with a trial design, she conveyed a legitimate concern about being excluded from potential benefits of a trial drug and her account reflected the principles of a 'crossover trial[6]'. Several informants who had agreed to take part in a crossover trial viewed this design as a *'win-win situation'* and a way of '*attempting to please everyone'*. While the cross-over design appears to be primarily advocated by trialists as a strategy to increase the safety profile of trial drugs, informants who had direct experience viewed this and similar designs as intuitively fairer and as ensuring they were not missing out on something potentially beneficial.

While informants accepted the necessity for placebo trials, they expressed varying concerns about the ethics of such trials and some were more inclined to perceive them as a potential '*waste of time'*.

[6] A crossover trial involves a trial in which participants receive a sequence of different treatments. For example in a design which involves 2 treatment arms all participants will receive a period on both treatments (NIH, 2014)

It's always difficult with placebo trials and in the past I know my parents have sort of said no we aren't doing it because you do have to sort of take the additional treatments but it might not be doing anything, or you could be on the other half of the trial where it's a massive benefit, and I have always wondered about the ethics of those kind of trials[...] Megan (26y)

5.4.2 Practitioners' perspectives

For some practitioners, optimal recruitment necessitated a personal position of equipoise, clearly communicated to potential participants.

As an investigator, you should be in equipoise, and actually, you should convey that to the parents. Doctor 9 (child)

In the context of somewhat '*straightforward trials'* such as TORPEDO-CF involving two standard treatments, practitioners indicated that they found the concept of equipoise '*reasonably easy to explain'*.

I really genuinely don't know which one is better and the reason behind the research study is to try and find out if one is better than the other one. Doctor 10 (child)

Connected to the concept of equipoise was the need for practitioners to explain the process of randomisation which they generally didn't find 'a *problem'*. However, some practitioners recognised potential difficulties in explaining this term and helping patients to understand it.

Very much depends on the patient and their level of education, their level of language their understanding and so on. I think, as health care professionals we

generally… or a lot of the time overestimate people's literacy and numeracy, and there is … I am sure that a lot of the time we… pitch things at the wrong level for people, whether that's making things too complicated or, or dumbing down too much, it's very hard to get that right because everybody is different.
Doctor 12 (adult)

Practitioners often drew parallels with how tailoring the information concerning trial design was comparable to the difficulties practitioners face when adapting any medical terminology, which needs to be in accordance with a family's *'level'* and needs. In the main, practitioners viewed most individuals, including children, as able to understand that the allocation to particular arms of the trial would be made by chance or at the very least children could understand that their doctor would not be responsible for making that decision. Practitioners also reported that explaining the concept of placebo trials is largely unproblematic.

The easiest way to explain it is that there's a tendency for children to get better without doing anything […] quite a number of children will get better if we do nothing at all, so what we want to do is work out how many would have got better, if we hadn't done anything and see how many more than...would have got better just on their own? And try to explain it that way, but again, that's never an issue.
Doctor 3 (child)

However, some practitioners pointed to concerns about 'fairness' in relation to placebos, particularly that they might be regarded by some patients as *'unfair'* or at least less attractive than a trial comparing active treatments.

People have tried to organise studies in CF looking at chest physiotherapy and saying well let's randomise people to doing chest physio and not doing chest physio.

Now although there is no evidence for chest physio, intuitively it makes sense if you have got someone with thick sputum and you bash their chest they will cough it up. And, they couldn't recruit people, because people would say how we cannot do chest physio, no. Doctor 5 (child)

Some practitioners implied they would try and *'sell'* the placebo design as something positive in relation to increased monitoring and a '*regression to the mean*'.

If you get the placebo, well it won't make you better, but actually being in a trial sometimes, gives us a closer view of your CF disease and that in itself can be helpful. Doctor 6 (adult)

We try and sell it as something positive, I am not sure anyone has bought that [...] the study is quite clear that if you are in the placebo, you know placebo arm of a trial, you do better than the historical norms, and the presumption is because you know you will be having increased monitoring but not sure that patients buy into that. I wouldn't say it to everyone, but I do say that quite regularly to patients. Doctor 7 (adult)

Other practitioners implied that the concept of fairness and unfairness in the context of placebo trials was becoming more of a '*concern'* in the wake of the recent *'wonder drug trials'*.

Placebo is a concern, and probably more so recently, there's often this discussion of fairness and unfairness [...] it's harder and harder to justify placebo versus drug A if drug A is perceived as the marvelous new treatment already, in a build up that's gone on the internet. So having the ability to swap onto drug A at the end makes recruitment easier. Doctor 6 (adult)

One practitioner indicated that there had been a '*deliberate buy-in'* to trials which finish with an open-label period in which all participants receive the active drug, as a solution to concerns surrounding fairness. Practitioners viewed this design as providing a way of assuring that all participants have a *'chance'* to access the trial drug. Practitioners implied that the design removed some of the uncertainty inherent in more conventional RCTs, where patients might be left wondering whether they were on the active drug or whether the treatment had any effect. Practitioners indicated that this design had both a moral and scientific appeal, which in turn, had the potential to improve recruitment rates. One practitioner, who was the most enthusiastic about this trial design, viewed the traditional RCT design as a '*lottery'*, which was something he didn't want for his patients.

> *The company have said, the first so many finishing the study will get access, and I've said, can we make it clear whether our patients will or won't because I don't want them to be in a lottery[…]So having the ability to swap onto drug A at the end makes recruitment easier.* Doctor 6 (adult)

While practitioners spoke of explaining the principle and procedural aspects of clinical trials as largely unproblematic, they recognised the underpinning uncertainty about not knowing '*what is best'* as something that some patients had difficulty accepting in a health professional who had *'umpteen years of treating CF'*. Some also reflected on doubts they had about their personal position of '*genuine equipoise*'. One accepted that her experience of treating pseudomonas infection a certain way had left her struggling with equipoise in the TORPEDO-CF trial. While this practitioner recognised that the treatment standard for pseudomonas at her centre might not be *'right'*, she was concerned about deviating from '*aggressive'* treatments which she had witnessed produce positive results over the years.

We have got a very healthy population, we do very well, so we're obviously doing something right, so then to change it, you don't know what you are changing and you know somebody who is a bit iffy with treatment, who you then think well you can't get away with your IVs because you are in, you know you just give them that head start I don't know but, but I do appreciate that you know, part of antibiotics especially nephrotoxic drugs and stuff in the long term is not good, so you do have to weigh that up and actually is their alternatives it's just, I don't want you to use my population to find that out. Nurse 7 (child)

Some practitioners appeared to contend with the uncertainty presented in trials, by positioning it as comparable to or on a continuum with the uncertainty inherent in all medical care.

When you are dealing with clinical interventions even if it's not a research project you still have to sort of give some kind of ownership and empowerment to the people that you are talking to […]Rather than just saying well I am going to give you this and it's going to work, I would say look there is this other treatment this is the evidence behind it, these are the good things, these are the potential side effects, but in my opinion I think this is the right thing to do, what do you think? I think that it's a similar approach to recruiting for a research study, it's kind of well actually in this condition we know there is this drug, but we also know that there is this other drug and we don't know which is better, or we don't know whether giving nothing or giving this drug is better. Doctor 8 (child)

From this position, practitioners drew parallels between discussions required when changing treatments in the clinical context and introducing the possibility of entering a clinical trial. They positioned both situations as informed by evidence and with associated risks and benefits. However, the ability to provide an opinion and advice on the '*right thing to do*', while expected by patients in the usual personal

consultation context, was no longer available to practitioners within the context of a clinical trial.

5.5 Rationalising the costs and benefits

In this section I examine how informants' perceptions of costs and benefits relating to different research invitations featured in their view of a research fair offer.

5.5.1 Patients' perspectives.

Informants' perceptions of costs and benefits of trial participation were typically multi-dimensional, extending beyond the standard ones detailed in trial documentation. For the most part, adults and parents prioritised assessments of physical risk, which formed a critical 'cost' in the weighing-up process. Generally teenagers, and occasionally children, also prioritised a concern about potential risks to their health. For example, Ellie who had not yet been approached about clinical trials spoke about her reservations about participating and anticipated that she wouldn't be able to accept the element of risk inherent in many trials.

> *I just don't like testing because I just, I don't know really. I don't know I just feel like I wouldn't be able to trust it or like if it went wrong. Because I don't want to take the risks [...] I would like to help, but I just wouldn't want to, no.* Ellie (14y)

Clare indicated how her first concern was regarding a potential contraindication about her current medication and the trial drug.

> *Originally I was a bit confused about steroids and things because … I was like well is it going to have any effect with the other drugs [...]* Clare (17y)

For children who had not yet reached their teenage years, judgements of risk were less prominent or absent from their accounts generally and overall their conceptions of cost and benefit were less detailed. It is unclear to what extent these children were shielded from some clinical risks or the task of the weighing up process, or were unconcerned or were happy to defer judgements of risk to their parents

For children who did not discuss clinical risks, parent data indicated that the possibility of requiring extra blood tests was an important consideration. These younger children appeared reluctant to talk about the family's decision to decline a trial or study, despite their parents' encouragement. For instance Emily, who was happy to talk about her involvement in novel drug trial, also conveyed a reluctance to talk about the family's decision to decline the TORPEDO-CF trial. Whether children's concerns were dissipated through a positive participation experience or declining, or they were reticent about disclosing this fact, is unclear.

Parents who had involved their child in decisions about trials involving extra invasive procedures, for which they had consented, decribed how they had to *'play it really quite cool and calm and collected'* to explain the trial in nice simple terms. They suggested that if these negotiations were not carefully considered the child might *'latch on'* to a particular aspect of the study such as a blood test and then *'decide they are not doing that'.*

In contrast to children, in the accounts of adults and particularly parents their judgements of risk were keenly expressed as the '*first thing'* that came to their mind. For example, Jack's mother spoke of potential risks as her first most pressing consideration.

The first thing I thought was what if something goes wrong, what if he is allergic to it and they can't resuscitate him. I just spent six years of my life trying to keep this boy as well as I can, and within 10 minutes they have wiped it all out and initially I was a bit guarded […] Mother (Jack 8y)

Risks had to be offset or countered by benefits in order for informants to judge a research offer as fair. Characteristically the first benefit to be weighed in relation to potential risks was the possibility of an improvement in health from participating. On the whole, informants did not position the possibility of a therapeutic benefit as an expectation, but rather as a hope. They hoped they would receive some benefit or they hoped for a more general best personal outcome which was typically set towards the future. Interrelated with this was confidence that '*the trial made sense'*.

Rather than an exhaustive understanding of all the trial details, informants initially emphasised how the '*worth'* of the trial needed to be established before they would consider giving up their time or incurring any related costs.

If you are being asked to give up your time you want to know exactly what for, and what they are hoping to achieve […] you really want to know that it's worth it and that you want to know clearly what they are hoping to achieve. Megan (26y)

In the case of Jack's mother, the trial she was considering was fairly invasive, requiring regular additional blood tests. This risk was offset by the fact that the trial objective matched her concerns and was something she hoped would be beneficial for Jack in the future.

The impression I got was this drug would drastically, if it was ok, in the future, potentially make Jack's lung function, brilliant or a lot, lot better or stop it from deteriorating. And that is what I focus on with CF. The dietary stuff we can get

> *around but lung function, is massive to me and so I believed that if this drug was going to be ok for him in 3 or 4 years time, I wanted him to have that. I really, really wanted him to have that […]* Mother (Jack 8y)

An informant's typical, immediate hope for the best personal outcome remained fairly stable across accounts and trials, yet how individuals rationalised physical risk was more variable. Some adults described a systematic risk-based assessment based on the formal trial-related information. For instance, Alex described how he used safety profile data from earlier phase gene therapy trials to judge the potential risk of participating in a later phase one.

> *This was right towards the end of the trial, they had done it on I don't know, tens of maybe hundreds of people so if there was anything that they had found that went really badly wrong with it then you know they had been through quite a few iterations before it got to me [...]* Alex (29y)

Other informants rationalised perceptions of trial related risks relative to risks they had encountered within the clinical context or indeed risks they encountered in their daily life.

> *There's always a chance of something going wrong; you could get run over by a bus. It's I don't have any strong feelings about that.* Frances (63y)

Initial judgements of risk were capable of influencing an individual's receptivity to a trial, determining whether they would *'want to open themselves up'* to the idea of participating and could form a sticking point for other considerations.

> *The actual thing* [study] *itself, I can't remember what it was trying to find out, but it would involve something like, they'd want to shove a line into the vein in your neck and send that into your lungs to check something. They'd want to do a liver biopsy, a few other invasive things [...] I thought, it ain't worth doing you know.*
> Adam (19y)

Adam was invited via letter to take part in an observational study alongside his upcoming transplant surgery. However, his unease about the invasive nature of the study overshadowed his engagement with the aims and objectives of the trial or study. Furthermore Adam's pressing concerns about safety could not be allayed in the first instance due to the nature of the initial approach, which was via a letter from an unfamiliar hospital. In a situation where an individual had declined, potential risk was often the hurdle they could not get past. For instance, Phil described how despite a nebuliser trial being sold as '*the new big thing'* a safety profile of '*0.01% chance risk'* would still constitute a *'nagging'* level of uncertainty for him. He viewed his concern *'that he might just be the one in a million'* to experience an adverse reaction, as both '*stupid'* and '*human nature'*. Phil related his heightened sense of risk to his deteriorating physical health and a lack of adequate reassurances about safety provided by the recruiting practitioner.

In contrast to Phil's heightened sense of risk one parent, whose daughter had experienced a life-threatening anaphylactic reaction from a widely used antibiotic, recognised that things could equally '*go wrong'* within the normal clinical context. This parent talked about how any drug, taken for the first time, equated to a '*bit of Russian roulette'* whether within a clinical trial context or a treatment context.

> *Things can go wrong, but things can go wrong on drugs that have been tested and used for years, so, I mean Becky's had one anaphylactic reaction to an antibiotic, I could then argue that well clearly that's not a safe drug if that's what it's going to do to her, but it saves millions and millions of other people [...]* Mother (Becky 4y)

Many parents who had consented to the TORPEDO-CF trial recognised the relative safety of this phase IV trial which was comparing two '*tried and tested'* standard treatments. A decision which was viewed as being equivalent to treatment decisions they had to make on behalf of their child.

> *Last winter we had to decide whether to try a last-ditch antibiotic or send him straight in for his bronchoscopy. Which was scary for us because he was only 10 months old, and we went with the medicine rather than sending him for that [...] Yes it's the only sort of decision I suppose I can compare it* [TORPEDO-CF] *to [...]* Mother (Dylan 2y)

In fact, for one parent in this situation indicated that the process of randomisation provided a welcome relief from the usual burden of decision-making in the clinical context. This parent described "*how it was much better that* (the decision) *was taken out of her hands*" and "*it made more sense to leave it up to fate*".

For parents with no prior trial experience, recent clinical experiences often informed judgements of risk and benefit. The most prominent example was a parent who drew on a recent '*traumatic*' clinical experience involving her son's first blood test, to inform her decision to decline the TORPEDO-CF trial and thus avoid the IV arm of the trial.

> *When he started going on about needles and stuff, he had a bit of a bad time getting bloods out of him, so I didn't want to put him through it again [...] it was just traumatic for him[...]* Mother (Tom <1y)

This parent described herself as still coming to terms with her son's condition and she did not identify any immediate or future benefits for herself or her son through participating in the trial. Also, she used the term '*guinea pig'* to depict the invitation, conveying a feeling of distrust; and was concerned about making a decision on her son's behalf. Moreover, her invitation to take part in the trial was the only approach which involved a telephone invitation by an unfamiliar practitioner whom she never met face- to face.

Adults also discussed how the intensity of their recent clinical experiences, including the number of blood tests or hospital admissions they have to cope with combined the '*additional poking and prodding'* required for trial participation, was influential to their willingness to participate. *Mia* described how she had declined all the trials she had been approached about primarily due to the significant costs of trial participation including additional invasive procedures and extra trips to the hospital to her usual treatment regime.

> *I've been approached about a lot, there was one where it involved, it was a new nebuliser for like so many weeks, and every week you'd have had to get, I think every couple of days at the beginning, and then every week it was different breathing tests you'd have to go up to the hospital and have done, and there were bloods, and there were all sorts [..]my veins aren't good and it's quite, it's not that easy having a blood test when they can't get the..any blood out of your veins. [...]* Mia (25y)

For some, the potential change in a current treatment regime which may impact on health status, rather than the risk associated with the trial drug and procedures, constituted a risk not worth taking.

> *What I would have had to stop was really working, still really works now so I wouldn't have liked to have chanced and take a chance and not do it and then get ill again so[...]I felt a bit bad like I would like to have done it, but at the same time it is not worth risking it.* Luke (22y)

Informants' acknowledged that risk varied from '*study to study*' and low-risk trials were generally considered easier to decide on. However, higher risk novel trials with great promise were often prioritised by informants over more run-of-the-mill trials. Accordingly, adults' and parents' accounts illustrated how they were prepared to *'stretch'* their child or themselves and negotiate higher levels of risk than they would normally accept for trials which offered great promise. For example, for one family in the context of a novel trial relating to a potentially revolutionary new drug, which they believed '*could be huge*' or possibly *'life-changing'* for their child, they were prepared to accept their daughter having to '*overcome a real phobia'* related to venipuncture .

> *With the blood tests, the two visits because she was screaming and crying, they could not force her to do it. And we nearly, very, very nearly weren't able, and I had to say to Emily, "Look, you're going to have to calm down, if you want to do this trial and be part of it you need to calm down because the minute the consultant says we can't continue, there's no going, "No, no, I want to do it now, once she's gone we get on that train we go home," and she was old enough, mature enough to calm down. And even though she still cried, she let them do it. So I said, for an eight-year-old to overcome a real phobia.* Mother (Emily 9y)

Similarly in the adult context Kate explained how she had some initial '*reservations'* concerning the degree of risk and burden connected with a gene therapy trial, but was prepared to raise the stakes on this occasion due to its potential significance. In spite of this, the trial costs had proved greater than she had anticipated and with hindsight she probably would not have accepted the invitation.

> *It was really exhausting there were so many tests, and up and down to London all the time, I don't think I had fully appreciated it [...]There was so much work to do and you had to through lots of really quite not very pleasant tests and I don't think if somebody asked me again to do the same thing I don't think I would do it, because I found it really hard.* Kate (29y)

This sentiment was echoed within other informant's accounts, in which the actual trial burden had exceeded their expectation. For some informants the unanticipated costs of a trial had lead to their subsequent withdrawal. For instance, Tim had agreed to take part in a Mannitol[7] trial, perceiving it as a fairly low-risk. However the trial had turned out to involve intricate, time-taking procedures requiring Tim to carry large volumes of medication (a sentiment echoed by another informant who had dropped out of the same trial).

> *I did a Mannitol sugar trial; yeah that was a pain in the backside. It took me an hour in the morning to do and an hour at night to do. I had 30 capsules I had to empty and breathe in, and it just took so much time. [...]I did it for six months and I then said to the CF centre look, I know it was a nine month trial, I said I done six*

[7] Mannitol is an osmotic agent available as a dry powder to be used as an inhaled drug for treating lung disease in cystic fibrosis (Flume et al, 2015;Nolan et al, 2015)

month, I really can't do anymore, you know I just cannot afford the time to do it [...] Tim (49y)

Patients and families had often been asked about trial participation more than once and sometimes, particularly in the adult setting, on numerous occasions. Thus, in addition to assessing the costs and benefits for each trial or study it was not uncommon for informants' to refer to a broader weighing-up process in relation to a cumulative research responsibility and a perception of '*doing their bit'* and not being overburdened. *Megan,* who had been approached many times both at the paediatric centre and adult CF centres, spoke of attempting to '*balance out'* the distribution of research burden or responsibility.

I have always tried to balance it out if I have said no to one or two I have said yes to another one […] Megan (26y)

5.5.2 Rationalising costs and benefits: practitioners' perspectives

Consistent with patients and families, practitioners' judgements concerning safety were central to their views of the ethical acceptability of trials and their personal commitment to them. Assuring patients of safety was a priority for the positive marketing of a trial. The research regulatory system provided an important '*selling point'* for potential participants and *'protection'* for practitioners themselves. However, practitioners indicated that the research system was not infallible and one practitioner recalled how a trial their centre had been involved in had actually done '*more harm than good'* and had failed an '*interim safety review'.*

Consequently, while all practitioners accepted the need for a research regulation, their conceptions of risk hinged on additional personal and collective team

judgements of safety. Practitioners recalled occasions when the CF team had declined to take part in some trials *'sponsored by pharmaceutical companies'* as they felt the potential risks and burdens were '*too onerous'* for their patients. One practitioner spoke of how she would only feel comfortable approaching families about trials or studies that she would feel comfortable recruiting her own children to, and indeed, she had recruited her own children to clinical studies and trials within the hospital. This practitioner drew on her experience as a parent to consider the fairness of the research offer.

> *There are studies that I've had that I wouldn't have recruited my babies or children to and I think that's a big thing if, the studies I've worked on I would recruit my children to all of them […] I think the biggest selling point is, if you wouldn't recruit your own child to it, I wouldn't expect anybody else to [...]* Nurse 3 (child)

She also explained how she had identified trials that had not met her personal benchmark of acceptability, and she recalled that one of the trials failed to recruit any families.

At times practitioners' assurances of safety or being free from doubt appeared somewhat at odds with the inherent uncertainty within clinical trials.

> *I wouldn't ever start a treatment where I really didn't think it was safe.*
> Doctor 3 (child*)*

> *If I have got doubt, then I should not do this for my patient, so you need to know this study very well, you need to be very, very clear, if I have any doubts I will not do it for my patients [...] I do not want my patient to be exposed to an unnecessary trial, unnecessary pain, or uncertainty.* Doctor 2 (adult)

Nonetheless, their accounts were consistent with patients' expectations that practitioners would not suggest a trial that they really didn't '*think was safe'*. As well as assurances of safety, practitioners drew attention to parents' inclination to want or hope for the '*best return',* which they saw as being part of *'human nature'*.

> *It's human nature that if you are entering a trial, you would hope that you were getting that drug that may well make you better, wouldn't you really, but then by the very nature of consenting to it, you run the risk that you are not going to don't you.* Nurse 2 (adult)

Some practitioners indicated that where they believed there was a potential for personal benefit, this would be positioned as an individual '*selling point'*.

> *You have got to find the selling point for each individual patient. Now sometimes there isn't, and I am honest enough to say to them look, for you, it might not make any difference at all, but in the long run, you know in the future.* Doctor 5 (child)

Nonetheless, they acknowledged that trials could not guarantee personal benefit and even in those trials which had more potential of personal benefit, this might only constitute *'minor benefits'*. One practitioner spoke candidly about how trials are '*rarely a great' opportunity'* in terms of clinical benefit as '*most of the pharma stuff is a bit of me-too'*[8]. This practitioner believed that for a trial to represent something he could view as a great opportunity, it would need to involve '*new revolutionary drugs'* that could potentially *'transform people's lives'*. In contrast some practitioners viewed

[8] 'Me-too' drugs also referred to as 'follow-on' drugs, comprise pharmaceutical products which largely replicate the action of existing products, contrasting with potentially 'pioneering' or 'revolutionary' drugs which are clearly differentiated from existing drugs (Hollis, 2004).

their belief in the potential of the trial drug as intergral to their construction of a fair research offer and a way of balancing their *duty of care'* and the inherent uncertainty in a clinical trial.

> *I've been the person that's been saying, "Here's this treatment, I think that will be good for you", so when I'm doing a, putting a study forward, they look at me, and they say, "Do you think this drug is worth it?" Now clearly, ethically and on the information sheet you know, so I say things like, look I wouldn't have agreed to do this study if I didn't think it would pass muster on the safety so far, but we are doing a trial and on the potential for it to work because I have a duty of care […]* Doctor 6 (adult)

I viewed this practitioner's comments, that the trial drug had the *'potential* 'to work as the counterpart to an individual's hope for the best personal outcome.

While equipoise is considered to be the ethical professional response to the uncertainty of a novel clinical intervention, practitioners' accounts reflected the delicate balance between the principle of equipoise and the pervasive psychology of hope. Which was captured by a practitioner's quote below, when asked about the importance of equipoise in relation to his commitment to a trial.

> *I wouldn't want to be involved in a study where I didn't believe that one of the medicines was better than the other [...].* Doctor 1(child)

Given this practitioner's extensive knowledge and experience, I was inclined to view this position as equivalent to a belief in the *'potential for the trial drug to work'* rather than a misunderstanding of the concept of equipoise. These findings illustrate

that while the principle of equipoise is considered essential for the ethical conduct of a trial, a degree of hope in the therapeutic value of a new drug is equally necessary to embark on a trial or deem the study acceptable for their patients. Practitioners, like patients, rationalised inherent trial uncertainty with hope for the best personal outcome.

5.6 Assessing trial burden

In addition to assessing the direct physical risk associated with trial related procedures informants also considered trial related burdens when constructing their view of a fair research offer.

5.6.1 Patients' perspectives

There were some notable divergences with regards to adult, parent and child perceptions of trial burden. In the main, adults placed the most emphasis on potential trial burden, with a focus on time constraints. An adult typically positioned '*time commitment*s' as the most important consideration in determining whether to accept a research offer, once the issue of risk had been rationalised. Their accounts illustrated how they were not only managing typical activities of daily living but were also managing a life-limiting health condition requiring demanding daily treatments regime. Not only were objective time commitments important but also how these time constraints could be negotiated and how much the '*big asks'* of trials were *'taken into account'* in relation to individual circumstances and work commitments.

> *I think what comes across and it's been my experience throughout actually is they don't take into account ever your life or lifestyle, so I work, I work full time, I have*

nearly always worked full time, and they say oh well we would just like you to come along for this, well that's a day off I have got to take [...] Phil (35y)

When you're approached about a study a lot of the time, they just see the CF side whereas you have got the life outside that as well, which it can affect and, you know, especially if you're working. A lot of them are big asks. Mia (25y)

Participants described being willing or more inclined to '*find the time*' if the recruitment approach was '*done right*'. For example, Gareth talked about how a trial involving a time commitment of '*only 15 minutes a day*' was unlikely to be ever be perceived as that for someone with CF and suggested such requests needed to be handled sensitively.

Yes this is only 15 minutes a day or whatever [...] it's making it easy rather than saying right we have got this trial, it needs 15 minutes a day, you know you must be able to find 15 minutes, and you just sit there and think… go away, leave me alone don't you tell me when I can find 15 minutes. Gareth (40y)

Accounts also suggested that 'the *right trial*' had the potential to lead an individual to *'find time'*. Studies involving minimal time requirements, that were viewed as being *'rolled up into clinic'*, and not requiring any '*major commitment'*, appeared to promote interest or accessibility, being seen as something which did not encroach on personal time.

Some adults also talked about how *'time is money'* and suggested that the expectation that someone should volunteer their body for testing free ran counter to societal expectations where few things are free. Consequently, for some a financial incentive or reimbursement was considered an important component of a fair offer,

serving to '*soften*' time lost. Other adults, however, while acknowledging the significance of time and economic constraints, expressed concern about the possible ethical tensions in relation to a financial incentive, which might encourage people to sign up for a trial for the '*wrong reason'*. For others, the combined potential personal costs, including economic, financial and time constraints constituted a too great burden to be offset by financial reimbursement alone.

While some parents talked about the logistics of balancing the needs of the family unit including work and school commitments and caring for other children, their focus on issues of burden was much less prominent. Furthermore, parents generally did not refer to the practical burdens typically detailed in patient information, including *'added inconvenience of additional questions and extra clinical visits'* (TORPEDO-CF PIL, 2010). Indeed additional clinical monitoring was positioned as *'a big plus point'*. Trial procedures also offered to reduce responsibility for maintaining or improving their child's health status, through the process of being '*double watched'* and *'checked'* throughout.

Teenage accounts largely resembled adult's accounts, with teenagers more inclined to frame their decisions around whether trial participation would be worth the time and effort.

> *I was just worried about whether it was actually going to work or not and I just thought well if I come out of it at the end and find that it hasn't worked I will feel a bit like Oh well that was a bit pointless. I didn't really want to feel like the whole thing was just a waste of time.* Clare (17yr)

There were some obvious variations concerning children's perception of trial related procedures or potential burden. Nonetheless, some of these issues appeared to impact on their receptivity to future research invitations'. For example, having to miss school was perceived as a burden for all the parents and some of the children, however for others '*days off school'* were viewed as an '*upside*' to trial participation.

> *I would say yes because you get days off school and everything and you get to play.* Daniel (11y)

Several younger informants also viewed the trial experience as being *'fun'*. The source of children's enjoyment in the trial experience appeared to be connected with: meeting '*new people'* and the social relationship developed with the trial team; the novel element of trial participation; parents ensuring the trial experience was made *'as good as they could'* with additional special treatment such as gifts or trips out; and facilities at the Clinical Research Facility [9](CRF). For children who were able to have their '*normal'* clinic visits at the CRF, this was described as an influential factor in their positive view of trial participation, with trial visits seen as more enjoyable than routine clinical visits.

> *They're better than just ordinary visits because ...you do a lot more fun stuff. You don't need ... there's lots more stuff to do, and it's a bit more chilled out[...]And it's fixed into the normal one, they do the stuff that you normally, like get weighed and stuff.* Daniel (11y)

[9] CRF's comprise part of the NIHR research infrastructure by providing dedicated purpose built clinical spaces in which expert staff can deliver high-intensity experimental research in the UK (NIHR UKCRF Network, 2016).

Children spoke positively and enthusiastically about the resources available at the CRF which included a '*DS'* (a popular dual-screen portable game system); a '*Pool ta*ble'; '*TV . . . and it's got whatever you want on'; and 'Wii' (*a home video game console). Rachael described a hospital admission and the restrictions required to stop cross-infection as a point of comparison to highlight the appeal of the clinical research facility.

> *You don't have to be in the same hospital and be in one room, a little room, you only have to be in a little room and just a TV and a bed and some colourings, but there you have got a pool table its massive, you can do what you like there, and there is no people that are separating you in the room.* Rachael (10y)

Boredom was identified by both parents and young people as a potential burden or *'downside'* of research participation particularly at centres where no CRF were available.

> *One time you could have been there for 3 hours, another time you were there for 5, another time you were there for 7, it was a long , the full day basically and that was a long a long time, you were getting bored really, weren't you, the length of time that some of it took, that was only the downside really.* Mother (Peter 12y)

However, for the most part children like their parents perceived a number of aspects of trial participation positively rather than burdensome.

5.6.2 Practitioners' perspectives

Practitioners' judgements about patients' vulnerabilities to trial risks and burdens varied across child and adult settings and influenced their view of who best to approach. Adult practitioners emphasised increasingly intense treatment regimes, deteriorating health and employment commitments as important vulnerabilities to trial burden. These practitioners were empathetic with regard to how research might be perceived by some adults as another burden and expressed ambivalence, reluctance and occasional avoidance of approaching some patients.

> *There was a few that were probably eligible but we didn't approach because we didn't think they would either go for it or they wouldn't adhere to it or because there was a lot of work in it, or we didn't want to burden them even more than they were burdened already with their care.* Nurse 5 (adult)

Adult practitioners also highlighted potential *'psychological barriers'* which they felt were more prevalent in the population of adult patients and which had the potential to exacerbate their concerns about research burden.

> *Some of them do have psychological barriers because it's usually that they are diagnosed as babies, and they have grown up with the CF, and they do get baggage and they do have psychological problems [...] anxiety and depression is very high as you can understand you know if you have got a life-limiting illness especially when they transition over from paediatrics to us because they don't really generally now lose children as in paediatrics but obviously they die in adult care, so there is a huge issue when they move over to us.* Nurse 6 (child)

This practitioner draws attention to an important historical change in end of life care in CF, as this now occurs almost exclusively in the context of adult care rather than in paediatric settings, due to improving life expectancy for people with CF. By contrast, while paediatric practitioners considered the impact of trial burden on the patient and family they emphasised the physical risks and how '*the little ones, they all hate blood tests'*. Indeed, the invasiveness of *'needles'* was highly prominent in considering the burden of trials for very young children, compared to adults.

> *I think paediatrics is different to adults because with an adult you would just say I am going to take some blood, and off you go but with children with a five year old there is a lot of preparation, that is needed before you just dive in with a needle.*
> Nurse 4 (child)

In cases where the child had a needle phobia or past traumatic clinical experiences, some practitioners spoke of trying to pre-emptively offset any burden from the trial by offering families ways of overcoming such difficulties. This might involve the use of Entonox (medical nitrous oxide and oxygen mixture) or play specialists to address needle phobia.

In the context of commercially funded trials practising '*competitive recruitment'*[10], practitioners described how investigator site target samples might often be small, and there may be more eligible patients than there are trial places. In this context, one practitioner commented that to suggest an invasive trial to the parents of a

[10] Competitive recruitment works by pitting investigating sites against each other, to create an incentive for practitioners to recruit patients as fast as they can. In return for involvement in the protocol and remuneration , investigators agree to recruit a specific number of patients(often within a specific time period) (Caulfield, 2006)

'*needle-phobic six-year-old'* would be '*totally unfair'*. Consequently, this practitioner indicated she would use her knowledge of the patient and family to assess the degree of trial burden and the fairness of an approach.

> *I think you really then have to pick patients. There was once this trial where the kids had to have eight blood tests on day one and eight blood tests on day two because that was very well known that that was a very kind of invasive study, they got a lot of money for it [...] I have no problems suggesting that trial in particular to 14-year-old boys where I know they can make their voice heard. And that's fine, but I would have a problem approaching a mother of a 4-year-old boy for that trial because he will be totally traumatised afterwards and you know why would they want to be in that study in the first place if you see what I mean? I think you sometimes have to be a bit, what are we trying to get out of it? And it's really the patient benefit is paramount.* Doctor 4 (child)

In the context of large multi-centre trials, practitioners were more obligated to approach all eligible families. Nevertheless, one practitioner described how the team '*probably steered a family away'* from participating in a trial, at a time when they believed the trial burden was too great for them. This 'steering away' rather than not approaching an eligible family at all seemed to reflect a situation where the practitioner made sure patients were fairly selected and their own obligations as a researcher were upheld, while still ensuring a duty of care.

5.7 Summary

When faced with the choice of participating in a trial, adults, parents, practitioners and some children engaged in a comparable '*weighing up of options'* or a '*weighing up of pros and cons*', which reflected how informants made sense of the cost-benefit

balance of a trial or study. How individuals rationalised risk, made sense of a trial, evaluated its 'worth', and the adequacy of the information given, were prominent features of this discourse. Informants who had consented to a clinical trial typically viewed randomisation as something they tolerated, giving precedence to their perceived value of the trial and clinical research in general. For the most part, informants prioritised risk and anything that may '*jeopardise*' their own or their child's current health status. It was also notable that informants, who were reticent about research or had declined research offers, were more risk averse. Furthermore, individuals with a deteriorating health status and extensive treatment burden, in general, emphasised judgements of burden and potential risks.

There were also some parallels with normative ideas about decision making and risk in informants accounts, which at times mirrored a 'rational' and deliberative account of how they made sense of research invitations (Hardman, 2009). Informants indicated that they were prepared to negotiate higher levels of risk or burden for trials which offered greater promise or could even be potentially *'life-changing'*. At face value, this model appeared to be an important element of informants' construction of a fair research offer. However, it is uncertain to what extent individuals were complying with expectations of the informed consent process, which advises that '*it is important for you to understand why the research is being done and what it will involve' (e.g. TORPEDO-CF information leaflet, 2010)*. While many individuals framed their judgements of cost and benefits around the trial information, knowing the information was only one facet of how they made sense of the process and was not always necessary to establish what they viewed as a fair research offer. Moreover, expectations concerning cost – benefit ratios were not fixed and varied within individual accounts of the same trial, according to different trials and the social context in which invitations were made. This process also took

on different forms and emphasis depending on an individual's sense of responsibility and personal perceptions of fairness in relation to the costs and benefits of a particular trial. Paralleling modern theories of cognitive psychology, these findings illustrated how informants' rational and experiential systems appeared to operate in parallel with interplay between intuitive and more analytical systems (Slovic et al., 2004).

CHAPTER 6: FINDINGS
WHEN IS A RESEARCH OFFER FAIR? - A SOCIAL DISCOURSE

6.0 Introduction

This chapter focuses on the relational aspects of the encounter between the potential 'participant' and recruiter and the social context of the research invitation, which together I define as a social discourse. For brevity, I refer to this initial invitation to take part in clinical research as the 'approach'. The construct of trust featured prominently in this discourse. Taken at face value it provided little insight into the qualities necessary for the establishment of 'trust' or the processes involved, therefore the findings presented in this chapter sought to identify separate factors contributing to an individual's perception of trust. In the first section I consider patient and parent perspectives concerning the social context of recruitment, which appeared to inform their conceptions of trust, followed by an examination of practitioner perspectives. Later in the chapter, I illustrate the centrality of trust with regard to the ease that patients/families felt at being approached and how trust featured in their subsequent participation decision. In the second section I examine practitioners' discourse relating to trust.

6.1 Impact of relationships: patient and family perspectives

Relational aspects were prominent in the accounts informants gave of how they viewed an initial invitation to consider participation in a clinical trial and their judgements concerning the value of the trial.

6.1.1 Familiarity

Research invitations typically occurred within the routine clinical format across both adult and paediatric settings. Patients and families indicated that the regularity of clinic appointments, which took place at least every 6-8 weeks, had led to them feel accustomed to these interactions. For the most part, children, parents and adult informants who knew the practitioner before the approach, valued the relationship. Many accounts portrayed the ease, comfort and reassurance they experienced when recruitment occurred within a familiar clinical context.

Some adult informants also recognised the clinic as a '*convenient format'* in which to raise research, and that approaches made within the routine clinical context constituted the most effective and practical use of everybody's time and resources.

> *When you go to clinic you, you see a multitude of people. You see a dietician, you see a physiotherapist, and then you see doctors, and so it was in between the visits that I was approached. So it wasn't infringing on my time, I was there anyway. It was in between people coming in, so it didn't seem like a, a nuisance or anything like that. It just seemed like you're saving me from sitting around really […]*
> John (33y)

Many informants perceived members of the CF team, as '*like a friend'*, someone *'who knows you really, really well'* and someone who they *'trusted'.* Their accounts illustrated how they felt reassured in their presence, portraying an encounter which they perceived as being *'easier'* and requiring less effort than meeting someone new. Consequently, this familiar 'model' of recruitment was viewed as something that couldn't be improved.

Amy's consultant, he asked if we would be interested no pressure, they always give you the choice and a full explanation and freedom to choose [...] they have got it just right, I don't see how you can improve on it. Mother (Amy 16y)

For many patients and parents, this was the only 'model' that they had ever encountered when being approached about research and it was one that they described largely in positive terms, showing a preference for a context they were familiar and comfortable with.

It's nice that it's the consultants that you know very well because the team do become like an extended part of the family because you do see them so often [...] They're [the CF team] *almost like my safety blanket, they make me feel secure and with them approaching me I feel more able to ask questions, talk to them, because they know you and they know Emily yeah, they know all of us [...]* Mother (Emily 9y)

I would prefer to be approached by my CF team because I feel comfortable when they come and ask me. Because I don't want like some stranger coming up and saying ah, we have got this rah, rah, rah, would you like to do it, I would be like wow, who are you. Ben (16y)

The necessity for *'specialists'* who they did not know, to approach them in the research context was also accepted. In this situation, individuals emphasised the importance of '*someone you don't know*' being introduced by '*someone you know'*, which they viewed as an endorsement for the trial and the researcher and *a 'matter of courtesy'*.

Some individuals who only had experience of recruitment within this familiar clinical context formed preconceptions about how it would feel to be approached about research by a '*stranger*' or a '*random person'*. In these accounts, which do not appear to relate to any actual research encounters, informants imagined what it would be like to be approached by a stranger about clinical research, and reflected on past clinical interactions with practitioners that they did not know. In doing so, they drew attention to communication styles, or interactional qualities, which they had come to value and expect during consultations, which may not be guaranteed in an unknown practitioner.

Informants, who had experience of engaging with new researchers, also identified corresponding interactional qualities, to those they had come to value within existing successful clinical relationships, which they also valued in the research context. Together these accounts portrayed prominent socio-emotional qualities of the recruitment interaction which informants viewed as integral to an optimal approach. Furthermore, these accounts also conveyed an expectation that the clinician in the "inviting" situation should go the extra distance to ensure that these qualities were part of the research context to optimise their recruitment experience.

6.1.2 'Feeling comfortable'

Feeling *'comfortable',* at ease and able to ask questions were identified by informants as essential ingredients of a '*reasonable'* approach. Informants talked of *'feeling comfortable'* as distinct to the establishment of '*rapport*' in clinical communication, something which was already present in the routine clinical format.

When meeting a new practitioner for the first time, several adult informants indicated that rapport could be facilitated by a practitioner's acknowledgement and

appreciation of an individual's depth-of-knowledge about their condition as opposed to a 'Dr knows best' approach.

> *The problem you get is that they've done their so many years of being a doctor, and they're a doctor, and they're better than you. But, actually, they have no idea, they haven't got the depth of knowledge I have about CF, so they can get lost, really. So if they already come in with a bit of respect for me and give me a bit more, give me that rapport maybe, you know, to say, or acknowledgement [...]* Helen (34y)

Other informants spoke about the significance of a personable approach rather than just focusing on '*the facts'* and clinical details.

> *Just have a kind of more human approach, rather than the whole clinical doctor way of, well of some doctors, you know, the way they go about things, of just facts and, you know, "This is what it is, and this is …" You know, sometimes it's nice to just soften it.* John (33y)

> *I think they've got to have a bit of personality, and I think they've got to be quite a people-person, not just, oh, this is this, and this is this, and any questions? I think they've got to know how to approach it because I doubt that - with like dealing with a hell of a lot of medical people over my life, like it really makes a difference how you're approached[...]* Mia (25y)

These accounts conveyed the significance of interpersonal qualities of research invitations to avoid discussions seeming like a ritual involving the disclosure of '*just the facts'*.

Some informants indicated that feeling '*comfortable*' with a 'softened' approach was more important than simply knowing the practitioner. This view was very notable

in the account of a teenager who emphasised how while she felt comfortable with some practitioners, there were others she knew who she did not feel comfortable with. Her account of a recent approach about a clinical study, conducted by an unfamiliar practitioner who had put her at ease and made her feel comfortable, illustrated that this informant placed a higher value on the ability of the recruiting practitioner to put the individual at ease, over familiarity.

> *I felt comfortable with the* [practitioner] *who was talking about it I was like yes[...]He was a laugh, he was funny, you could have a laugh and a giggle with him about it […] because he asked me what my thoughts were, and I said a day off college and he thought that was quite funny. And he goes yes that's what most people have probably said a day off college or a day off school[...] I think that is more important, if you can have a bit of a giggle with them, or if you feel comfortable to talk to them about it, then it's, yes.* Kirsty (16y)

Younger informants also echoed this sentiment and appeared particularly open to meeting new people. However this openness was in part conditional on 'niceness'. Furthermore, this disposition seemed to be partly based on past successful engagements with new researchers. Younger informants described these new practitioners as '*nice people*' who they had come to view as their '*friends*' and people who they had enjoyed spending time with. These successful research engagements seemed to result in an open attitude to the prospect of meeting more new researchers in the future.

> [name of Dr] *asked me to do it and I agreed and then I met these nice people [...]It wouldn't matter if it wasn't brought up by people I knew [...].* Rachael (10y)

Who would you like to ask you about studies in the future...have you got a preference who you'd like it to be?
Lots of nice people. Emily (9y)

6.1.3 Feeling valued and being part of something of value

Adult patients emphasised the significance of practitioners conveying a shared understanding of living with a '*serious illness day in, day out'* on top of general day-to-day demands. For the research exchange to be viewed as equitable their already constrained time needed to be sufficiently appreciated and employed in something worthwhile, to ensure they weren't wasting their time.

Informants perceived there was a 'right way' to approach people about research, which ensured people felt in control and understood.

> *It has to be the selling aspect has to be done right and it… understanding you have got a lot on your plate if you work and your treatment, but there is a way of selling it to somebody that makes them want to do it. Because, you sort of you are not saying we need you to do this, or we want you to do this or… or you are helping by doing this, it's like well you know if I understand, the more understanding you show to somebody's situation the more willing they are going to be to participate, or actually to find the time. And I think that's it and it's sort of putting them in a… almost in a position of control.* Gareth (40y)

While many parents acknowledged practitioners' consideration during approaches, parents tended to focus more on the value they placed on being able to be part of something worthwhile. Parents who viewed their invitations as trouble-free described feeling '*honoured*', '*lucky*' and '*privileged' to* have been invited to take part.

So that's the first time we did it, but we were kind of… we didn't feel privileged, but we felt like we were helping. Mother (Jack 8yr)

I did feel quite honoured, yeah, when, and that was the first one we'd been approached about. Mother Emily (9y)

Children's illustrations of feeling valued were less explicit than those of adults and parents. However, child and teenage informants spoke of feeling *'excited'* or *'special* 'at being invited to take part in a trial, conveying a sense that they understood they were engaging in something of importance.

What did you think about being asked about that study?
It felt quite fun because I was really excited to be one of the people that tested a tablet. Emily (9y)

I think when he mentioned it was going to be a trial I was kind of, oh, kind of excited. Amy (16y)

Rachael recalled how she was the first participant in Europe for one of the trials she had taken part in, conveying a feeling of special status. Also, some younger children spoke about undertaking special activities during trial visits, or being given treats by their parents during the research process, which also legitimised the value of their actions.

Every morning before we went up to the hospital, we always went somewhere in the city to look at stuff. Emily (9 yr)

The good thing about it is when it's dinner time they give you an hour or so and afterwards you can go to the museum or so for an hour, and I get an ice cream […] Rachael (10y)

Adult and parent informants emphasised the significance of being approached face-to-face, reading this as a sign of the value of the trial.

*I feel if a doctor or a nurse hasn't got time to come and ask you as an individual, then they shouldn't be putting it out like that. So if somebody couldn't come to me face to face and ask me, then I wouldn't want to know.[...] I wouldn't think it was worthy***.** Mother (Kirsty 16y).

I think this goes for quite a lot of people, I think generally life is quite a busy thing to do, especially now, everything's getting faster, people have to be up longer, work longer, you know. There are more things going on, so there's less free time. So people are less inclined to take that time out of their daily routine and do something like a clinical trial, unless somebody approaches them because then they kind of feel special I think, and they feel like someone's taking the time to ask me, so I'll take the time to give it back. Adam (19y)

By making the time to come and ask them individually, practitioners demonstrated not only the 'worthiness' of the trial itself but also that they the valued and respected the family or individual being approached. Consequently, approaches that did not involve a carefully considered face-to-face approach did not reinforce a sense of being valued. Therefore postal methods or trial advertisements were conveyed as devaluing both the study and the individual, creating a situation that individuals viewed as '*not worth*' pursuing.

I thought it was bad that it came in a letter as well. Because I didn't have, there wasn't even a contact number. There was an email address, and that was it [...] there was no contact number to check, there was no-one even… you know, face to face or over the phone or anything. I thought it ain't worth doing you know.
Adam (19y)

Families and patients felt more reassured about the value of a trial that was introduced by a known practitioner, compared to actively responding to trial advertisements or trial websites even if these were displayed in a familiar setting. One parent anticipated she would feel more personally responsible for any negative outcomes of a trial that she had '*gone out*' and found, compared to one that was introduced to her by a member of the CF team. Informants only spoke of being proactive about research in the context of revolutionary '*wonder drug'* trials, such as gene therapy or comparable novel drugs, where the value of such trials had been widely reported in the media.

6.1.4 Being provided with reassurance

Informants highlighted the importance of the interactional nature of the encounter in which individual fears, or worries, could be identified and addressed by practitioners. This quality was distinct from feeling comfortable and at ease and was directly related to a practitioner's ability to identify anxieties and provide necessary reassurances and was viewed as having the potential to influence their receptivity to research offers.

When meeting a new researcher for the first time, a practitioner's manner and expertise provided informants with '*peace of mind*' regarding the practitioner's competence and the quality of the trial.

I think it's important that the people that are asking are kind of very approachable people, someone that can explain things and able to answer questions well, and sort of able to listen you know and actually say have you got any problems or have you got any questions and just be very knowledgeable really but in a sort of friendly way. Megan (26y)

For some individuals, the seniority of the recruiting practitioner instilled confidence in the quality of the trial.

Having him telling you, because he's the most senior I don't know I think we felt a bit - I don't know if safer is the right word - but you know you've kind of got the top man for the job advising you and talking to you, so yes you feel like it's safe to kind of make those decisions. I think if it was just a nurse or you know, it'd be different, I would sort of demand to see someone of his stature to talk about it really. Mother Dylan (2y)

Being approached in person by a practitioner, who was aware of their medical history, was also viewed as reassuring with regards to the relevance of the trial, something which could not be guaranteed when responding to a trial database or website.

I recently had a look at the CF Trust website I was like well I don't know if I fit into any of these categories you know sometimes it was a bit vague as to what sort of person they wanted for the trial, so although I had a look I didn't really like respond to any of the you know… there was none that really caught my interest, whereas if your doctor recommends it to you then you know he has already thought about it, so maybe it's better to come from the doctor. Molly (24y)

Children's accounts' illustrated how they felt unconcerned or supported during research invitations. This lack of concern appeared to be due to the reassurance derived from the usual format and setting of the invitations, which included the presence of their parents and typically a familiar practitioner.

> Mother (Rachael 10y): *The other main Doctor who you see quite a lot broached this one*.
> **Rachael:** ***She is supportive to me***.

Some older teenagers had begun attending clinic appointments without their parents, or the idea had been raised as something that would be introduced in the near future. However they spoke of valuing the reassurance they derived from their parents' presence and most teenagers indicated a preference for them to be present during clinic appointments and when being approached about research.

> Mother (Amy 16y): *They ask Amy now rather than ask me, ask Amy through me, they ask Amy directly now.*
> **Amy:** ***I still rely on you. I always prefer mum there. If I get stuck, I just look at mum, and she just knows what I am thinking [...]***
> Mother: *But I also don't want people to think that I am butting in and I am talking*

Furthermore, some adults and occasionally parents described seeking additional reassurance and support from their own parents when approached about research, with some parents of adult informants regularly attending clinic appointments.

The significance of sufficient reassurance in an emotional context was highlighted in parents of infants' accounts of their invitations to participate in the TORPEDO-CF trial. For all these parents, this was the first trial that they had been approached

about. The clinical eligibility for TORPEDO-CF trial involved an individual testing positive for a serious bacterial infection of the lungs - *pseudomonas*, which can lead to permanent lung damage if not eradicated successfully. Consequently, the emotional context of the approach was one of concern for all parents as they were aware of '*how horrible pseudomonas is'.* Parents described being '*shocked'* and '*worried sick'* which was especially intense for parents for whom this was their child's first episode of *pseudomonas*. Nonetheless, being approached face-to-face within the context of an existing clinical relationship was viewed as providing the necessary reassurance for these parents, to the extent that the experience was relatively unproblematic for them.

Alice's mother described how a practitioner who knew the family well, was able to support the family and address their particular needs and concerns, enabling an unguarded interaction, which may not have been achievable with a '*complete stranger'*.

> *It was reassuring, the nurse that was there to meet us is one of the CF nurses that we know really well, and she understood our kind of anxiety and was very reassuring [...] it can get a bit much when you see new faces all the time [...] you can ask questions that you wouldn't necessarily ask somebody that is doing the trial, because you know them and you know that they are going, to be honest and give you truthful answers, and they also know what sort of people we are, so they knew how we would react to being asked about the trial and they knew what Alice's' dad's main concern would be [...] because I think if it had been a complete stranger they wouldn't have known our situation, or how you know because Alice's dad and I are very different with how we deal with the whole CF, so they know that he gets quite anxious about stuff[...].* Mother (Alice 3y)

For some parents, the knowledge of the trial appeared to act as an emotional buffer, something that helped to counter the emotional *'shock'* of finding out about their child's infection, resulting in her feeling '*more determined to be part of it.'*

> *I was still reeling from finding out about the pseudomonas, to be honest but yes, I think it kind of made me more determined to be part of it* [TORPEDO-CF trial] *[...] So I think it does help to be honest. If you are faced with that situation and you know there are drugs available that can help, and that there are people researching this to see if they can get rid of this altogether [...]* Mother (Isabel 2y)

In contrast, several parents of infants described being approached initially about the TORPEDO-CF trial via telephone by an unfamiliar practitioner as something that '*could have been handled better'.*

> *It came as a shock to find out about the pseudomonas, so that first phone call was a little bit of a information overload, you know [...], so it seemed very rushed. I think maybe, not so rushed would've been a bit better or you know if he'd just said that, this has been raised, could you come in, you know pop in and see me, have a coffee, chat about it [...]* Mother Dylan 2yr

> *Someone rang me and just asked me about it [...] They sent like booklets out and stuff, on It [...] I would have liked someone to come out and speak to me one of the CF team probably, someone that I know from there.* Mother (Tom<1yr)

> *If it's a total stranger, you know, you just think first of all you're taken a aback by, oh, someone's phoned me up about a trial and, you know, it's a lot to take in […] I think it would have been better for us if our CF nurse had as I say, because we've got a bit of a relationship with her and, you know, it would have just reassured us.* Father (Harry 1yr)

The reassurance and comfort provided in person, or by someone known and trusted from the CF team, appeared to be the qualities that were absent from these approaches. Consequently, these parent accounts portrayed how in this context they felt '*taken aback*' and found it difficult to raise concerns, perceiving the information about the trial and the infection as '*a lot to take in*'.

This was offset by their belief in the importance of clinical research as the overriding factor in their decision to take part. Nevertheless, the deliverance of an optimal approach was more likely to be critical to the construction of a fair offer for individuals who were ambivalent, unsure, or comparatively less favourably inclined to clinical research.

For instance, Tom's mum who declined to allow her child to participate in the TORPEDO-CF trial was the only informant in the sample whose recruitment experience consisted of two telephone calls with no face-to-face discussion. While this parent cited the most influential factor as her preference for the oral arm of the trial, due to a recent '*traumatic experience*' involving her son's first venipuncture, she also spoke of not wanting her son '*being used like a guinea pig*'. This parent's use of the term '*guinea pig*' appeared to reflect her misgivings and unease about the unfamiliar research context. It is plausible that with a more conducive encounter, involving a face-to-face meeting with a known CF practitioner, an improvement she suggested, her trust may have been gained and some of her concerns may have been allayed.

6.1.5 Downsides to familiarity

Depite the clinic being a convenient format for research invitations, patients and families also described the clinic as a busy, often demanding, time where they may

not be as likely to take the time to think about research, or show an interest. Some adults also described how approaches made directly in the clinical context could feel slightly pressurised. Staged approaches involving being forewarned about a study in advance, before being directly approached, for example by receiving a brief introduction and patient information leaflets at the end of the clinic, or with clinic appointment reminder letters, were suggested as strategies to allay any sense of pressure felt with direct approaches.

> *I like the fact that you got the letter you know and it provides a lot of information and you know you can think about it before you go to clinic rather than… sometimes in clinic, you could feel like you have been put on the spot.* Kate (29y)

Research invitations within this routine setting, when the conditions were right were often portrayed as being relatively insignificant as almost a 'non-event.'

> *'When you're approached, and you're fine with it, it doesn't feel like anything*
> John (33y)

The familiarity of the clinical context appeared to have lessened the significance of the approach and the distinction between research and clinical encounters, resulting in the approach becoming a 'non-event'. This view was noticeable across all sub-groups but emphasised in adult accounts. Adults had the most long-standing clinical relationships with members of the permanent CF team and typically had received more invitations to participate in clinical research compared to parents of younger children. It is therefore plausible that these individuals had become more habituated to negotiating research invitations within the routine clinical context.

Some adult accounts appeared to reflect the tension between wanting the approach to be the unpressured and non-intrusive usual 'model', and also wanting an approach that conveyed both the worth of the study, and the value of themselves as potential participants. One informant described repeated occasions on which he had been approached about research '*on the fly, on the day*', a circumstance he indicated was not well considered or thought out. While he felt comfortable saying no 'as *they were never precious about it in that sense*', this approach appeared to have influenced his receptivity to the idea.

Similarly, Sara another informant implied that due to the familiarity of the clinical context, despite feeling at ease with the circumstances of the approach, which involved a CF nurse who she described as '*like a friend'*, she didn't feel she had *'actually'* been approached. For this informant, being given leaflets via her CF nurse, rather than by someone she perceived as a member of a research team, did not in itself appear to constitute an approach about research.

> *I haven't been really approached. I've been given leaflets, but I didn't really read them if I'm honest [...] There's probably just been one or two, and again I think, I'm sure that was through the CF nurse, so no one physically approaching me.*
> Sara (30y)

Children who commented directly on their experiences of trial or research discussions typically described approaches about research in quite neutral terms as something that *'doesn't really bother me'*. To a certain extent, these findings resonated with adults' accounts of the approach as a *'non-event*'. Nonetheless, children, particularly younger children, provided the fewest details with regards to the approach and it formed the least prominent feature of their accounts. There are

several explanations for this finding. Firstly it could be that these children had little involvement in the initial approach and subsequent discussions. Consequently, the approach was not salient to them. This assertion seemed the least probable, as all parents went into detail regarding the extent both recruiting practitioners and they themselves had involved their child in research discussions. Also, parents spoke of encouraging their children to participate in this study about trial recruitment, which would seem counter-intuitive if these young people had been excluded or given little involvement in the recruitment process. What seems the most probable explanation is that from the child's perspective, research invitations made in a familiar context lessened the significance and the distinction between research and clinical encounters, combined with a child's preference to delegate decisions about their CF to their parents. Added to this, some approaches were made sometime before the interviews took place, so some younger children may have struggled to remember the event.

Problematic existing clinical relationships also led to some ambivalence about this familiarity 'model' of recruitment. For instance, one adult informant described how he had been reluctant to accept a research invitation from a known clinician whose communication skills he viewed as inadequate. For this individual despite having known the recruiting practitioner for some time, he viewed all the approaches he had experienced from this clinician as *'disengaging'* and had declined them all.

> *No, he was a complete bumbling arse to be fair, and that switched you off a bit. He had no bedside manner at all [...] well the major problem with that particular, is he was just terribly patronising and he was just really disengaging.* Phil (35y)

The potentially negative aspects of an approach involving an existing relationship with a practitioner were highlighted directly by one parent who was also a qualified nurse.

> *It's difficult really because I know some CF teams do their own research anyway and I know of an incident another CF mum I speak to [...] she's actually moved his care now because she felt that the consultant was only treating in a certain way because of his research, she just felt his care was being sort of moulded to suit the research that was going. I think external sources doing clinical trials and things is probably better, I think just to say stop sort of biased results [...] I think I'd question it more if it came from the team, just because I'd feel like well "Is it their research, or is it an external source doing the research?" I'm just suspicious like that I think myself.*
> Mother (Becky 4y)

She described the importance of separating clinical research from the clinical team and was very conscious of being unduly influenced by a known member of the CF team. In spite of this '*suspicion*', she also recognised the complexity of the situation, stating that *'somebody's got to mention it'.* Furthermore, she recognised how an '*external source'* in the form of a '*stranger with a clipboard'* might not be ideal for a *'major clinical trial'* and there may be a need for a *'more personable approach and a bit of familiarity'*.

The quote below highlights tensions between feeling at ease with a known practitioner while implying that it may be easier to say no to someone you don't know, or that the obligation to say yes may be greater in the context of an existing relationship.

> *It would be good to have maybe a mixture so you could talk to someone in your team about exactly what it is and get more detail and information and you might ask them questions that you perhaps wouldn't ask a stranger you know but I think maybe it's good to sort of you could actually have that neutral person there, that you don't, you know don't have a connection with and you can say well no I am not interested in that.* Megan (26y)

However, no adult or parent informant described feeling any direct pressure from the CF team to consent. In addition, accounts illustrated that informants were aware that they were '*definitely within our rights to say no'.* Equally, no child indicated that they felt under any pressure from either practitioners, or their parents, and all but the youngest positioned themselves as having an active share in the decision-making. This finding was corroborated further by all parents, acknowledging their child *'has to have a choice whether he wants to take part or not'*.

Nonetheless, some informants suggested how '*saying no to somebody in the CF team would be more difficult'* compared to an unknown researcher. While others, suggested the converse situation, viewing saying no to a practitioner who knew them and understood their situation as *'less awkward'*. Several adult informants implied this familiar context might have precipitated their decision to decline. Also, several parents noted that because the trial had been offered to them by a member of the CF team whom they respected and trusted, this signalled that the CF team thought the trial was the best option to take. Furthermore, some informants spoke of wanting *'to give something back'* to the CF team for the gratitude they felt for receiving the '*best care available'*. However informants' motivation *to 'give something back for the care you've received*' appeared personally located, rather than connected to the actions of the CF team. Adopting 'a mixture' of someone from the team and a *'neutral person'* with no *'connection'* was suggested as a solution to balancing this noticeable tension.

6.2 Impact of relationships: practitioners' perspectives

6.2.1 Familiarity

A comparable social discourse was evident across practitioners' accounts. Resembling patients, they acknowledged that recruitment usually occurred within an existing relationship or closely connected to the clinical context. Practitioners also suggested it would be *'strange'* to do anything else within a '*stable population who the team knows very well'*. In the context of these long-standing relationships practitioner assumptions closely mirrored those of patients, believing patients would expect, or even express, a preference to deal with people '*who they knew'*, at least in the first instance.

For the most part, practitioners viewed approaching known patients about clinical research as easier and less '*awkward*', compared to approaching someone unknown. They spoke of this in the same way that clinical communication, in general, would feel '*more comfortable'* with a known patient. Several practitioners expressed reluctance or ambivalence about giving that responsibility away, implying it would not feel fair to the families or themselves as a practitioner.

> *I wouldn't want to give that responsibility away. I know the family, know the background; the family knows them as well and so having that element of trust that is already in place. [...] If it's someone that you don't know then the family might well say well what does C1 say about it, you know or what do the permanent members of the team say about it. So I think they would often, the families know the consultants all really well, they know us all by our first names, so they would, they would often expect that we would be involved [...]* Doctor 10 (child)

However, other practitioners assumed that in the security and familiarity of the CF clinic, where conversing with a variety of '*medical people'* was the norm *'one more person'* would be '*nothing heavy'* for many patients.

> *They are used to coming to clinic aren't they are used to meeting medical people they are used to being in that environment and it's a lifelong thing for most of them [...] so it's just one more person that is going to pop in and have a word, so there is nothing heavy about it.* Nurse 6 (adult)

Comparable to patients, practitioners acknowledged the importance of the unfamiliar researcher being introduced by a known CF practitioner to foster receptivity and instil '*confidence'* in both the recruiter and the trial.

> *It takes a long time to build relationships up with CF patients, and they don't like change, so a new face coming in can put the barriers straight up. And so I would go in and say look this is one of the girls you know, I am virtually saying I support her on what she is doing and you know I can stay in with you or I can leave and they go no, no, you go off and do it that way.* Nurse 1 (child)

Practitioners implied these introductions helped to legitimise the research as something *'credible'* and trustworthy and part of *'the system'* as opposed to being offered something *'leftfield'* '*out of the blue'* or 'off *Tin Pan Alley'*. Their accounts illustrated how these introductions conveyed both tacit and overt endorsements of the practitioner and the study, promoting an individual's receptivity to the idea of engaging with research. Indeed, one practitioner viewed this strategy as an ethical if not a legal requirement in most cases.

> *Coming from the team that know them first, has always got to be the way to do it, because in theory that's how it should be any way through ethics [...]it's better that way anyway if it's somebody they know and understand what their role in the system is, talks to them first, it always helps.* Doctor 3 (child)

When practitioners moved away from describing recruitment within the ease of an existing relationship, such as those typical in the CF context, it was something that became much more '*difficult'* and potentially *'awkward'.* One practitioner who was currently involved in mostly approaching patients whom he knew, something which he viewed as unproblematic, contrasted this role with the position of recruiting patients to '*acute studies'.* Within an acute situation, in which emotions are typically heightened, time constraints apply, and the patient is unknown, this practitioner perceived recruitment in this context as the *'coalface*' of recruitment.

One practitioner stressed the discomfort he felt when he had felt obligated to take the responsibility of recruiting to a study which '*effectively involved cold calling'* patients, identified through a database. For this practitioner, asking a stranger '*out of the blue*', disconnected from the clinical context, was perceived as something difficult compared to the relative ease of approaching a known patient within a routine format.

Despite practitioners identifying contexts which eased or challenged optimal recruitment, some indicated that the recruitment discussion was out of their '*comfort zone',* and that of most practitioners. While practitioners recognised how recruitment was easier with patients who they knew, they indicated that the change in dynamic in which they were asking patients to '*put themselves out'* or '*help out'* was the source of discomfort, not apparent during routine clinical consultations.

Some suggested that individuals involved in recruitment, particularly recruitment outside of an existing clinical relationship, required skills over and above those needed in the routine clinical context. A sentiment which was comparable to patients' expectation that practitioners involved in recruitment, particularly those not known by the patients would need to go the extra distance for recruitment to be successful. Their accounts also highlighted particularly qualities, skills or aspects of interpersonal interactions that they regarded as facilitators during research invitations and instrumental to successful recruitment.

6.2.2 Right person skills

Practitioners across settings viewed the tenets of competent clinical communication in routine clinical settings as guiding how research offers should be made. The significance of establishing rapport and initiating interaction before going straight into details of the study was highlighted by several practitioners

> *So you need to start this just almost like personal communication skills, then you start to know that patient a bit [...]* Doctor 2 (adult)

> *Often people go straight in with, I'm here, I'm doing this study, and I've looked at your notes, and you meet the, you know. It is about hello, tell me about your disease, do you know; get a bit of them talking first, and then the patient believes that you're interested in their disease.* Doctor 6 (adult)

Many practitioners felt the role of recruiting required the '*right person skills'*, which was comprised of exceptional communication skills. Despite the evident additional complexity of having to negotiate both the child and parent involvement in trial discussions, pediatric practioners regarded the ability '*to communicate at different*

levels at the same time' as an expected, almost taken-for-granted competency for practitioners working in child health. However, like the adult practitioners, they recognized how effective communication was essential for successful recruitment.

6.2.3 Facilitating a patient's sense of being valued

Corresponding with patients' accounts, many practitioners emphasised the importance of conveying a shared understanding of the patient's illness, in which they were both knowledgeable and empathetic during their interaction.

> *You've got to have a little bit of a knowledge about the background of the disease[...]Just because it gives you a general knowledge about the disease and the disease process and having some empathy with the child and the parent.*
> Nurse 3 (child)

Some practitioners emphasised the need to be as accommodating as possible to both offset the burden of asking people to *'put themselves out'* and to ensure individuals felt valued, which practitioners believed was 'especially' important in the context of CF due to their '*many problems'*. One practitioner implied that without an individualised approach, recruiting patients may become comparable to *'factory work'*, in which patients may feel like *'a number'* being used for the production of scientific knowledge, rather than being personally valued.

Several practitioners believed successful recruitment was conditional on an interactional encounter in which the practitioner can elicit the patients' values, concerns and priorities rather than '*simply talking to patients'*.

You just need to understand what their issues are, the same as a clinical consultation and most of the time doctors talk to patients and they talk about listening, but they don't bother. And, actually, that's what you've got to do. If you want to sort out the medical problems and recruitment, you need to listen to what they're saying and make sure whatever you say back addresses the concerns which they might be telling you overtly or covertly. But you've just got to work out what's important to them. Doctor 3 (child)

6.2.4 Tailoring and reassurance

Practitioners talked of the importance of '*preparation'* before the approach. Where possible this included finding out about any '*family nuances'* or '*difficulties,* being knowledgeable about the study and being aware of the patient's medical history and past clinical experiences.

I have already rehearsed in my mind what I will be saying anyway. I will, of course, want to know the background of the families […] anything that might colour their judgement about it. So there is definitely some preparation to be done.
Doctor 8 (child)

Several practitioners indicated that if trial discussions could be embedded within the '*clinical interface'* rather than a '*bolt-on'*, this dynamic had the potential to highlight the relevance of the trial, ease interaction and increase the likelihood that the individual would consent.

Normally raise it in the day to day clinic setting [...] In general, you can either do the business of the day, how they are, etc., etc. Having said that, sometimes it works better if there is a specific thing about that patient, like they're saying, I find these nebulisers troublesome because they're twice a day, although I do them. You can use

> *that opportunity to say... that's interesting because we've got a study and the companies have listened to us, and this is a drug that's once a day, and then it's, oh that's interesting, tell me about it [...]If there is a link, then I think you're more likely to recruit.* Doctor 6 (adult)

Practitioners felt that recruiting within an existing clinical relationship enabled them to tailor interactions according to individuals' needs, which made them feel 'a *little bit more confident'* during recruitment, this in turn helped a patient to have *'more confidence in them'*. Practitioners approaching a patient or family for the first time spoke of using either information provided by the clinical team to tailor discussions, or using medical notes to *'get the story straight in your mind'* and ensure they were aware of any particular issues.

> *I would be given the information and anything I might need to know [...] I would very much do it on what the [clinical practitioners] terms were actually so it might be for example that… a family is having trouble adjusting, or it might be the family is having trouble with school [...] so I tend to be kind of be guided by what the other professionals tell me really, who do know the families.* Nurse 4 (child)

Unlike doctors who '*had a reason to be talking to the patient about their condition'*, research nurses did not appear to have at their disposal the same '*clinical lead in'*. In contrast, these practitioners described shadowing outpatient clinics, making themselves available to patients and being introduced to patients by known practitioners, so they were viewed as being part of the clinical team.

6.2.5 Downsides to familiarity

Practitioners whose primary role was the provision of care, while they accepted the need for research also recognised that without additional '*back-up*' from specialist researchers, it was both frustrating and unworkable to manage both roles effectively. One nurse recounted her frustration at missing potential recruits for a study during clinic because she physically did not have the time to see everybody and clinic duties took priority.

Practitioners expressed ambivalence about their *'dual role'* where they were required to '*wear two hats'*, that of a practitioner and a researcher (which I examine in more detail in the section on trust). To address these concerns, some practitioners advocated a combined approach involving both the clinical team and outside researchers working in partnership as the best strategy for successful recruitment.

> *It's good to have both because that way hopefully you can capture the wider audience, but I think by having the specialist* [practitioner] *involved as well, she knows the patients inside out, and she will be able to… or he will be able to know who would be suitable to be approached by a stranger, and who needs to be approached by the nurse that they know them… bearing in mind their whole background and their history.* Nurse 5 (adult)

This approach ensured a wider audience was captured while also tailoring approaches to meet patients' needs.

6.3 Trust and a fair offer: patients' and parents' perspectives

Integral to an informant's view of a fair research offer were explicit or implicit portrayals of 'trust' in social relations and the broader social system in which research invitations were situated. These perceptions of trust were not only viewed by informants as something which increased their receptivity and engagement during trial approaches, they were also seen as something which off-set risks and uncertainty associated with trials and instilled belief in the value of the trial.

It was evident from informants' accounts that interpersonal trust was predominantly related to past and on-going social relations within the clinical context, involving practitioners responsible for caring for themselves or their child. One parent described what this concept of trust meant to her as follows:

> *It feels like you are going to fall backwards and you have got a big soft bed to land on, they are that strong and united as a team, and everyone is involved, you haven't just got one person, that looks after you, everyone is involved in it. And even though there are lots and lots of children that they look after with cystic fibrosis they still make you feel like an individual, you know like they are dealing with you and not a number of people. And they come out… a phone call away basically I will phone them, and they will be out the same day […]they will just come out for reassurance and to make you feel happier, yes. I have built up that… that trust with them really and I go with anything that they say because they wouldn't do anything to harm her, to put her in harm's way, or anything and they are working towards this… this goal as well the same as everybody else.* Mother (Isabel 2y)

In describing trust as something which had ' *built up'* over time, this mother illustrated a feeling of resilience and depth; and this depth of quality was paralleled in other adult and parent accounts.

> *Obviously, we've got a, a big trust with the CF centre you know, and over the years that, you know if, I wouldn't be here if it probably wasn't for the CF centre so, you know, you've got to think that they're … obviously, they wouldn't do something to harm you. It would always be like, you know, something, that is to your benefit, so it was kind of like, you know I felt I had trust in that [...]* John (33y)

Perceptions of trust conveyed in adults' accounts appeared qualitatively indistinguishable from parents' conceptions of trust. However trust as a concept was much less apparent in children's accounts and was mostly implicit, except for older teenagers and therefore will be examined separately at the end of this section.

Parents' and adults' accounts illustrated an expectation or assumption that the same duty and quality of care would be applied by practitioners in both the research and the clinical contexts.

> *I feel more reassured because I know the individuals, who normally approach me, and I know how meticulous they normally are, and I know in any other respect of my care that they go through the right channels. So I think it, within the CF Team is particularly reassuring.* Craig (44y)

Informants believed that practitioners they knew, who were responsible for their care, would not knowingly put them at risk of harm.

He wouldn't allow anything that he didn't think was… that's what I feel anyway, I have never asked him about it, but that's the way I feel that he wouldn't let… if he thought it would if it were to harm you in any way, he probably wouldn't let you do it anyway. David (40y)

The fact that consultants were aware or directly involved in a trial or study instilled a belief, or expectation, in patients and parents that their own, or their child's welfare, had been taken into consideration and that the trial would be to their benefit.

I think that that was why he was offering us the trial was because he thought it [TORPEDO-CF] *was the best.* Mother (Alice 3y)

If you trust somebody, you're more receptive to what they say, because… I mean obviously, she sees a lot of patients, but you kind of have a belief that she wants what is best for Harry because she knows him as a little person, rather than just a number [...] Mother (Harry 1y)

This view is especially prominent in some parent accounts of children who were too young to be involved in the recruitment process and those who described never saying *'no to anything'*. For these parents, trust in the CF team appeared to be central to countering worries about doing '*what's best'* or the '*right thing'*. A belief that the CF team would *'ultimately do what is best'* for their child, was fundamental to their decision to allow their child to participate. Nevertheless, these parents also implied they accepted there were no guarantees.

I doubt they [the CF team] would consider it if they didn't think that it would be a benefit for one and for number two it would be safe because they are recommending it to you. So I trust that. Mother (Nathan 16y)

I suppose it's down to the trust again, isn't it. I would assume that Peter's CF consultant wouldn't put Peter through anything that is going to make him go worse, or anything that they do is going to be of benefit for Peter, it's not going to disadvantage. I hope that that is what it would be. So I think I would support them and go along with it, and trust their, what they say really. Mother (Peter 12y)

For informants who had declined research invitations, or those that had experienced stressful or less than ideal health care encounters, expressions of trust appeared the most tenuous and direct expressions of trust were either absent from or less notable in their accounts. For instance, Helen described feeling respect and trust for her current doctor but felt that over the years she had experienced certain inadequacies in her care and felt that this pervasive trust could cloud judgement on things and she described adopting a more pragmatic view over time.

What I now have found is that what I've realised, as much as I say about I've got my respect for my consultant, I've got my respect for my team, and I trust them. At the end of the day, I am just one patient out of 300 or a 1,000, whatever they look after [...] so I still have to think for myself, my consultant actually could retire tomorrow, or go to another placement. He doesn't think about me; he doesn't actually think actually Helen's relied on me for twenty years of our lives. You still have to have that realisation, and I think sometimes you get clouded with that. Helen (34y)

Parents and adult patients were also influenced by a broader institutional trust - trust in the NHS infrastructure, which incorporated the specialist CF facility; and

trust in the research regulatory system in place within the NHS and the pharmaceutical industry. Numerous parents had experience of working within the healthcare system, and these individuals emphasised their confidence in the research regulatory system, at the same time recognising how people who did not have the same insights might be more concerned about safety.

> *I know how difficult it is to do research and all the hurdles you have got to jump to even get the kind of ethical committee to agree to it and stuff, so I think that is more of a concern for Alice's dad that is, obviously it could be something that could end up being detrimental but, I have explained to him, and I know that it's impossible to even get agreement if there is even the slightest chance that it's not providing them with the best quality of care[...]* Mother (Alice 3y)

This parent, a nurse, believed that practitioners '*can't do research if it's going to be detrimental to participants health'*. However, other parents who were not health care professionals also echoed this sentiment of placing trust in the regulatory system as well as members of the CF team.

> *I'm pretty sure that the pharmaceutical companies wouldn't trial a medication on a child do you know what I mean if there was any major problems. I know it goes through lots of vigorous tests before it even reaches human testing [...]*
> Mother (Dylan 2y)

Some individuals viewed institutional trust as enough to instil reassurance about the legitimacy and quality of a trial, whether or not the person introducing it was known. One participant equated the CF centre to *'a little cocoon'* in which he felt safe in the knowledge that the CF team *'wouldn't let anybody just walk in'.* These

individuals also felt that if clinical research was raised other than on this '*familiar turf*', they would immediately be '*more wary*' and '*more dubious*' about taking part.

Furthermore, for some parents, trust extended to any research that was introduced to them via the CF centre. One informant reflected on how being approached in the familiar context of the CF clinic provided a '*subconscious*' assurance and personal motivation to take part. While this informant viewed himself as having a positive disposition to clinical research, he viewed research advertised outside of the CF setting as something he probably wouldn't be interested in.

> *You're more comfortable if it's done on familiar turf, like in the clinic, that gives certain assurance that the people approaching you are known by the clinic people, that's a subconscious thought really because I, I don't think like that, I don't give it any thought when somebody approaches me but I imagine that actually if it wasn't in that situation, maybe I'd feel a bit more wary […]I'd probably be a bit more wary about something that's generally advertised. I'd be less thrilled to take part in a study that had been advertised and was run completely separately. In fact, I wouldn't be interested, completely separately from the clinic.* Francis (63y)

6.4 Trust and family relations

For the most part, data showed that a child's trust or deference on parental direction and support was central to their ease with research invitations. However, some younger informants' conveyed a sense of trust, in both their parents and in their doctor, as being influential in their decision to participate.

Furthermore, some adults and occasionally parents spoke of depending on their parents for support with regards to research decisions. Adult accounts illustrated

how they drew on their every day decision-making patterns to make sense of their responsibility in the research context. For example, Mia described how all decisions she made in life constituted a *'team'* effort including her mother, her partner and herself.

> *We've always kind of worked as a bit of a team, and still now like I don't make a lot of decisions without talking to my mum about them. Just about anything, not just health-related [...] I think I need to talk it through myself a lot of the time, and just to hear if someone else says 'oh what are you doing? 'Or, 'Yeah, I'm doing it, and that's fine, that's a good idea', just that bit of reassurance, I think, so I still do that now.* Mia (25y)

In contrast, Megan saw the responsibility for research decisions as largely just hers, linked to her personal responsibility for managing to her own condition. However, she acknowledged that whether she would involve others in the decision-making process was, in part, determined by the potential impact of the research decision on those people around her.

> *I ask his opinion but I think as an adult the sort of major decision is just mine and I just take it you know whether I want to or not [...] because in the end it is my body and it's my condition [...] If it involved a lot of my time and a lot of our travelling up and down then I would obviously have to sort of say to him well you know what do you think about this but I think if it was something more sort of straightforward that I can just do without impacting anyone around me then I take the decision.* Megan (26y)

Nonetheless, unlike a child's reliance on their parent's support, an adult's reliance was not central to their decision-making process. For the most part, adult accounts

illustrated how they were accustomed to deciding for themselves in both the clinical and the research. Consistent with adult data, parent and child data demonstrated that the extent a child relied upon, or was directed by, their parents mirrored normal family patterns of decision-making which varied with the characteristics of the '*family set-up*' and their age and developmental stage.

> *I think it's your family setup as well because some mums I know are very controlling even if the child is like Ellie's age 14, I do know of some mums that the child doesn't go out, doesn't have many friends and just goes everywhere with mum.*
> Mother (Ellie 14y)

> *I suppose it's what kind of house you grow up in and what rules you have.*
> Mother (Daniel 11y)

For instance, when younger children illustrated being unconcerned and '*quite happy*' to '*go with it*' and trust what their parents had decided, their parents correspondingly positioned themselves as taking the lead role within the family situation. Nevertheless, the extent and nature of the youngest informants trust, or reliance, on their parents' direction in the research context were difficult to interpret through interview content alone. As younger children provided minimal, or no, detail about trial discussions. Even so, some insights into the nature of their involvement could be derived from parents' accounts and contextual data. One parent indicated how she had encouraged her son's involvement in clinical research, a pattern mirrored in the context of this study interview, in which she provided encouragement and support for her son.

> *I sat down and spoke to Jack about it, and we discussed it, and I said what do you think Jack and… he was very young but he didn't seem to mind he was a bit like*

kind of ok[...] He knew that he would be trying something and maybe it would help him when he gets older and… I think he kind of thought oh ok then [...]
Mother (Jack 8y)

Jack displayed an unconcerned awareness of having taken part in a clinical trial and deference and reliance on his mother's support and guidance. This finding was mirrored in the accounts of other younger informants and parents. Parents of older teenagers generally accepted that they were no longer in control and their children were no longer dependent on them. They positioned themselves accordingly, taking a *'back seat'* in the research context as they had done in other areas of their life.

She is nearly 17 she has got to make some decisions now, haven't you really, got to decide for yourself about lots of things. Mother (Amy 16y)

All teenagers indicated that they would still discuss research decisions with their parents and value their opinion even where they made the decision themselves. For older teenagers, conceptions of trust mirrored those found in adult and parent accounts, including references to both interpersonal and institutional trust. The oldest teenager, whose parents declined to be interviewed, perceived the decision as being shared between her and her parents, but she indicated that she trusted her parents to perform an initial level of screening to check the trial was reasonable for her to consider in the first place.

It was, both mine and my parents, of course, my parents had to discuss it first, to see whether they would want me to do it or whether they thought it was ok for me to do it, and then they would ask me, whether I thought it was ok. Clare (17y)

Consistent with adult and parent accounts, teenager accounts of interpersonal trust were connected to the duration and success of the relationship with the CF team. For instance Ben's trust in the clinical team provided his justification to '*always say yes'*, allowing him to acquiesce to these '*offers'*.

> *I know all the CF team, and I have known* [CF nurse] *for nearly 17 years, so there is that, whatever, I have practically trusted* [CF nurse] *with all the decisions she has made for me, and like whenever there is an offer like that, she has always asked me to see if I wanted to do it and I have always said yes.* Ben [16y]

Similarly, Kirsty's perception of risk was mediated by an assumption of trust in the medical profession.

> *Well they are doctors aren't they, you are supposed to trust them [....]thinking oh they won't put me in harm's way will they [...] the basics are you are a doctor, you are supposed to help people, so you are not going to give me something that is going to kill me.* Kirsty (16y)

Some parent and child accounts illustrated how family patterns were shifting. For instance, during one joint interview, a parent expressed concern at no longer being needed or entrusted with the responsibility of research decisions, prompted by both her sons developing independence and the CF team's encouragement that the child with CF does so.

> *And she* [CF practitioner] *said you do realise [...] age thirteen did she say, he is going to be getting called in by himself [...] to the doctors room by himself. And I feel like that's a hard thing, to be sort of discarded in a way shall we say, because you have always been there, you know they don't want to speak to you, eventually, they*

just want to speak to Peter, and then you will be brought in and told. And I know it's to get him ready to go onto the adult clinic she said, but I still think that is a hard thing to be told [...] to be, 'Oh Peter what do you think about this trial, don't worry what your mum says, we don't, she hasn't got a say in it, I think that is going to be a hard thing, to sort of go, hang on a minute, I am his mum [...]
Mother (Peter 12y)

At this point in the interview, this parent changed the focus of the interview to a direct dialogue with her son.

Mother (Peter 12y): *So how would you feel being asked to do a trial without me being there?*
Peter: *Don't know.*
Mother: *Would you feel that you are able to sort of speak up for yourself and decide?*
Peter: *Yes, but (...) but I would ask you, it would be better if you knew what it was and all that.*

During this exchange, Peter was placed in a sensitive position on hearing his mother's concerns about future changes, yet anticipated that he would be able to '*speak up and decide'* while still valuing his mother's involvement. Throughout the interview, Peter and his mother referred to changes in their patterns of decision making that were already afoot, with Peter becoming more knowledgeable and increasingly aware of his independence, while his mother was in the process of priming herself and Peter for further changes in how they would make decisions. Peter appeared to negotiate all these interactions sensitively with respect and concern for his mother's needs while conveying a clear sense of his developing independence. A similar sentiment was expressed within other children's accounts

in which young people were careful to uphold their parents' desire to be wanted and relied upon, illustrating diplomatic management of sensitive situations in which family roles were in transition.

These findings were supported by practitioner data which indicated that children in the '*in-between'* period, somewhere before the teenage years while being comparatively reliant on their parent's influence and direction were also in a period of transition. However, some practitioners inferred that depending on a child's stage of development and family pattern, children during this '*in-between'* period were generally more inclined to acquiesce to parental influence and take part in a trial that their parents believed '*they should take part in'*.

> *Mum's always in charge, isn't she, yeah [...] we're very influential, aren't we, as parents.* Nurse 3 (child)

> *If you're a nine-year-old kid and your parents really think you should take part in the trial, they make sure you take part in the trial, and you say yes, and you sign your consent form kind of.* Doctor 4 (child)

Consistent with parent and teenager accounts, practitioners viewed their trial discussions as more or less comparable to discussions with adult patients.

> *We have had some teenagers that I have spoken to about the trial, you know one would talk to them in almost the same way you would talk to the adults because they are very, you know they are very well versed in CF by that stage*
> Doctor 10 (child)

The influence of a child's family set-up on the nature of a child's involvement in the research context was inextricably linked to their developmental stage, personal experiences of clinical research and existing level of involvement in the clinical context.

6.5 Trust and recruitment success: practitioners' perspectives

Practitioners implied that in the context of CF they viewed clinical relationships as distinct from those in other contexts, owing to the longevity and intensity of these relationships in CF. They emphasised how knowing and caring for individuals with such a serious condition created an intense on-going clinical relationship. It had also fostered trust, albeit that this had *'taken time to build'*. Throughout their accounts, practitioners alluded to an *'element of trust'* as being central to the success of these long-term relationships and to '*recruitment successes'*, both regarding the ease of the recruitment encounter and the likelihood that an individual would agree to the research offer.

TABLE 6.1: The centrality of trust to '*recruitment success*'

The reason people go into trials, mostly, is because they trust the people asking them, on the whole […] Doctor 3 (child)
From a parent's point of view, I think if it was coming from somebody that they knew and they trusted clinically, they would probably feel more comfortable about saying yes. Doctor 5 (child)
Your recruitment success, always comes down to how much they trust in your judgement, if you say would you do this, and they trust you I think they often will do it, whereas if they don't know you from Adam, just some random person comes up they won't, you know they will say no. Doctor 7 (adult)
Our recruitment in a CF unit relates to if they know the people running the unit, trust them, and they are intimately involved, or even not intimately, but involved with the research. Doctor 6 (adult)

While practitioners recognised that patients often declined when they were approached by someone they knew or *'trusted clinically'*, they believed that patients would generally feel more '*comfortable about saying yes'* to someone they trusted. Furthermore, practitioners also assumed that patients would be more inclined to trust practitioners who had '*looked after them for some time'*.

Within the context of a trusting relationship practitioners also felt that patients were motivated by *'wanting to help'* practitioners as individuals.

> *The patients know me, they trust me and they will do things for me [...], and it's taken me a few years but now a lot of the patients know me, but it takes time to build that relationship [...], but I think it's quite a compliment that they know who you are and that they're wanting to take part and they're wanting to help you.*
> Nurse 3 (child)

> *They did it because they really liked her, and you made a difference to people and that, so for difficult studies, it's invaluable to have a, you've got to have the right person.* Doctor 3 (child)

While likability and trust were viewed by some practitioners as components of '*recruitment success'*, based on the assumption that patients are less likely to take part in a study if they did not like, or trust, the person asking them, other practitioners were concerned about this situation. These practitioners described unease with regards to balancing their research and clinical roles. This unease was manifested in practitioners' accounts as both personal discomfort about their position and anticipated concerns about how patients may feel. Some inferred that the change in

dynamic that existed during recruitment which involved asking them '*for a favour*', rather than the typical provider role, as the source of this discomfort.

> *I have found it a bit uncomfortable, that kind of that dual role and then asking them to take part, in a study and I think the reason it feels uncomfortable is partly because it feels a bit like asking for a favour, or for asking for some of their time[…]*
> AHP (adult)

A further concern expressed by some practitioners was a patient's susceptibility to overlooking the potential risks, in a context in which a patient's primary motivation to participate was to help out a trusted practitioner.

> *You have to really be careful because if you enter them in a trial there is a risk involved and you cannot guarantee there will not be any potential harm to this child and they have to be aware of that in many ways. And that's where you then think, like, I don't want you to do this as a favour to me. If you want it because you think it might be good and you want to help science and everything, then I'm really happy, but I don't want it just because I'm suggesting it and you feel obliged to do me that favour.* Doctor 4 (child)

In addition, several practitioners recognised that patients might feel pressurised in the context of longstanding trusting clinical relationships, arising from a sense of being '*indebted*', '*obliged*' or '*beholden*' to reciprocate for the care they had received. Practitioners also spoke of people who may view declining participation as somehow, *'letting you down if I don't do this trial for you*' or being concerned '*they might be treated differently if they don't want to be involved'.*

In the main practitioners described their principal means of countering such a sense of obligation was to put a great deal of emphasis on the voluntary nature of the request and to emphasise that declining would have no negative consequences.

> *The one thing I always stress and I usually stress it more than once when I am discussing things with people, is to say look you know, I promise you that even if you say no [...] even if you don't take part it's not going to make any difference to me, because I am still going to be your* [practitioner] *and I am still going to be looking after you, and I am not going to look after you any differently.*
> Doctor 5 (child)

Some practitioners spoke of the benefits of a *'clean researcher'* in which patients had no attachment, or dependence, on the practitioner responsible for recruitment. However, there was a converse situation that resonated with the perspectives of some patients, who felt more comfortable saying no to a trusted practitioner. Furthermore, in the context of an existing clinical relationship, one practitioner spoke in detail about *'protecting'* a parent from saying *'yes for the wrong reasons'* to an invitation for her 4-year-old daughter to participate in the TORPEDO-CF trial. This practitioner believed the parent, who had been initially approached by someone unfamiliar, had felt obligated to participate and this practitioner herself felt she '*was being pressurised to get her into the study'.* In this situation, she spoke of her duty to enable the mother to make a decision that was '*the right thing to do'* at that time, which in this case the practitioner felt was to start a course of IV antibiotics and decline the trial.

These findings illustrated both the perceived significance of trust in relation to '*recruitment successes'* but also the sensitivity of the situations where practitioners felt they had to tread carefully.

> *If you have got a good relationship with the family they trust you and I think that's so important that they will be guided by you but I know how far to go, not overstepping it.* Nurse 1 (Child)

6.6 Summary

A social discourse was demonstrated by informants' emphasis on the significance of feeling '*at ease'*, '*comfortable* and '*reassured'* during recruitment encounters and this was central to how informants made sense of research invitations. Furthermore, notwithstanding the variety of research experiences, considerable commonality existed within this discourse. In the main, this commonality could be explained through the impact of the social relationships within the recruitment encounter and the broader social context in which these research invitations were made. Trust was also central to how informants constructed a fair offer, which included interpersonal trust between participant and recruiter and the broader concept of institutional trust. Trust, as seen by the emphasis informants placed on being approached by a familiar member of the CF team who was responsible for their care, or their child's care, was significant in how informants made sense of the approach and subsequent participation decisions.

Patients and families gained reassurance by being approached about something non-routine in a context they were familiar with. Furthermore, the qualities patients and families had come to value and expect in a trusting relationship, provided

insights into qualities which had the potential to optimise the social context of recruitment. These qualities were the reason informants expressed a preference for research to be raised within an existing clinical relationship, and were also prioritised as integral to successful approaches by new practitioners. While an optimal approach alone was not enough to secure an individual's participation, successful approaches helped to maintain open, receptive attitudes to the idea of engaging with research and ensured future approaches did not feel burdensome. Many practitioners also highlighted the significance of competent clinical communication skills for *'sorting out'* recruitment and providing the framework for how successful research offers should be made.

In addition to providing comfort and reassurance for informants during the approach, trust also appeared to ease or lighten the load of shouldering the decisional responsibility, particularly for parents. Informants who had consented to trials typically couched ideas about costs and benefits in a framework of trust, which included both interpersonal and institutional dimensions and parental trust for younger informants. To what extent their trust in the recruiting practitioner allowed these informants to acquiesce to the invitation will be examined in the discussion. However, what is clear is that trust was pivotal to informants' satisfaction with the approach and their interpretations of a fair offer.

CHAPTER 7: FINDINGS
WHEN IS A RESEARCH OFFER FAIR - A PSYCHO-MORAL DISCOURSE?

7.0 Introduction

In this chapter, I will describe the findings which characterised the moral and psychological dimensions of informants' accounts of a fair offer. This psycho-moral discourse was by no means clear-cut and informants' portrayal of their decision to participate in a clinical trial was as a nuanced '*really personal decision*' in which moral and psychological dimensions were typically interlinked. This discourse was also closely interwoven with informants' personal weighing up of tangible costs and benefits associated with trial procedures (rational discourse) and the social context of recruitment (social discourse). Nonetheless in this chapter I aim to clarify the overarching patterns characteristic of this discourse

Central to this psycho-moral discourse was how informants worked to explain what they perceived as a research invitation which they felt comfortable accepting or in the case of practitioners one that they felt comfortable offering. This discourse was aligned with their personal moral identity and self- interests. Informants' who had agreed to participate emphasised the morality of their decision, viewing research participation as a common good, something they felt a sense of moral responsibility towards. They also emphasised the significance of hope and the maintenance of an optimistic outlook in making sense of their decision to participate. Practitioners also spoke of the importance of personal judgments concerning the '*morality of the study'* which enabled them to feel comfortable about approaching patients and present the study as a fair offer.

In this chapter I first present the patient and parent findings before turning to the practitioner findings. As convergences across adult and paediatric settings were prevalent in relation to this dimension of their accounts, my presentation of the findings reflects this by largely covering both settings jointly.

7.1 Patients' and parents' perspectives: a moral discourse

7.1.1 Research as a common good

Medical research was accepted by informants as a way to ensure that treatments continued to improve and advance, and they considered it '*a vital'* part of the medical profession.

> *I think it's needed; it's obviously needed and … without research you wouldn't move on really would you.* David (40y)

> *You have got to do it; you have got to progress because if you don't, you are not going to learn anything, nothing is going to be developed, I think it's massively important [...]* Mother (Jack 8y)

> *All this new stuff is less time consuming, so I can sort of do it on the way to school [...] I can see such a massive difference from when I was a little kid to now even.* Amy (16y)

Teenagers with direct research experience typically expressed a view which was consistent with parent and adult accounts. Children also conveyed research as something which had the potential to make them '*get better'* in the future and help them '*get well'* and viewed research as something essentially good. However, their portrayal of the generalised aims of research was often less prominent. Nonetheless

integral to informants' accounts was a broad acceptance of clinical research as necessary to sustain improvements in healthcare. A view which I interpreted as reflecting informants' overarching acceptance of clinical research as a common or public good, something they believed to be in the interests of all.

Informants indicated how their disposition towards clinical research and trials had developed over time and was something, which was continually being shaped by ongoing experiences and personal circumstances. Before being approached, or becoming more informed about clinical trials, some informants accepted that trials were something they hadn't *'taken an interest in'* or something they '*didn't particularly agree with',* often due to the prerequisite animal testing or personal costs involved. Faced with a new situation, they accepted that one's views '*just change on everything'*.

Not only did an informant's emphasis on their belief in clinical research as a common good shift according to their life experiences, but their views also varied throughout the course of an interview. For instance, one family, at the start of the interview highlighted their '*pro-research'* attitude as being influential to their commitment to '*wanting to help'* for the *'bigger picture'*. Following reflections on a burdensome first study for their daughter, their discourse shifted to positioning research as something that '*at the end of the day, nobody likes to do'*, and that the situation feels different '*when it comes to your own child'*. Those who had never been approached about a clinical trial or who had declined trial participation talked about clinical trials in less appealing or more ambivalent terms. These individuals described trials as '*technically beneficial'* or a *'necessity'*, and as something that involved more '*poking and prodding'* and '*being a guinea pig'*.

While informants accepted the necessity of clinical trials to generate medical knowledge, they also expressed caution relating to the inherent uncertainty underpinning clinical trials and the testing of new medicines. They illustrated an awareness of the negative public image attached to clinical trials and that not all were intrinsically good. Both parent and adults made references to what appeared to be the now-infamous 'Northwick Park trial'[11] and an awareness of the negative stereotypes often associated with clinical trials.

> Father (Harry 1y): *If you say clinical trials to somebody or trial, they think, whoa!*
> **Mother:** ***Yeah, guinea pigs, yeah.***
>
> *I'd seen things in the paper about it, a good few years ago there were some people all their heads had blown up like raspberries, you never read good things in the papers do you [...]* Father (Joseph 5y)
>
> *You occasionally get the odd horror stories in the press of drug trials and things, so I think these days there is always somebody who is going to come up with a horror story of something [...]* Gareth (40y)

For some informants, the value of research was reinforced by witnessing first-hand the introduction of new and improved treatments. Consequently, they were able to make a connection between progress in treatment and clinical research achievements, providing tangible endorsements of the value of research.

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[11] An independent phase I trial conducted by Paraxel involving eight male paid healthy volunteers. The six volunteers who took the drug experienced serious life-threatening adverse reaction to the drug being tested, with one volunteer experiencing severe swelling of the head (Vince, 2006).

> *DNase that's quite new to Amy now, and that is amazing, DNase is amazing stuff. And even like the physio techniques, have all changed now [...] but again that would have been trials, to do things like that.* Mother (Amy 16y)

Some individuals also spoke of the value of treatment advancements from research in relation to increasing life expectancy for people with CF, with many adult individuals describing how they had exceeded their predicted life expectancy.

> *The way it's progressed so much over the last I mean every year they have said life expectancy increases, and obviously, that is down to the medication and the care which changes obviously because people take part in research […]* Mother (Lily<1y)

Even though an individual's emphasis on the value of research was variable, an acceptance of clinical research as a common good, vital to ensure the progression of healthcare was evident across accounts. On its own, a positive personal disposition towards clinical research was not sufficient to amount to a fair research offer. Nevertheless, attitudes towards research did appear to influence initial receptivity to engagement with research and provided an essential foundation for an individual's construction of a fair offer.

7.1.2 A moral responsibility to contribute to a common good

Patients and parents accepted that research participation carried uncertainty, yet they recognised research as something valuable which '*has got to be done*' to '*make things better*' and *'improve things for the future'*. Some equated participation in research with charitable deeds and hence as '*doing their part*' for people with CF, comparable to '*sticking ten quid in a charity pot at the end of the week*'. Consequently, for some informants' their belief in the value of clinical research was positioned as

contingent on viewing an individual willingness to engage with research as a form of moral '*responsibility'* or social '*duty'*, in which everybody should try and do their share. The emphasis informants placed on a sense of moral responsibility to contribute to the common good was variable with some viewing research participation as a 'duty', '*task'* or even an '*obligation*', something that they felt they *'should do'* if in a position which enabled them to do so. The unifying concept within this discourse was the moral value informants assigned to participating in clinical research and a corresponding moral responsibility to engage with clinical research.

However, this view appeared to be complicated by the particular context of CF. Informants expressed concern that things might *'stagnate'* or stop improving for future generations if people weren't willing to participate in clinical trials. Informants also spoke of being '*grateful*' to imagined *'people'* who had contributed to the development of current CF treatments, feeling gratitude and a moral responsibility to continue to this '*cycle*' for imagined future individuals and families.

> *The fact that Harry is able to take part in it I feel that we're almost giving something back by letting him take part [...] Harry gets the treatment that he does now, because other people have undergone this sort of thing, and we're so grateful that people do, so of course we'd like do whatever we can [...]* Mother (Harry 1y)

> *The way I see it if people hadn't done trials, things like creon and different things like that, I wouldn't have benefitted, so I suppose it's part of the cycle really sort of trying to make sure that people in the future benefit as I have benefited from people in the past.* Megan (26y)

Some informants also offered a spiritual and philosophical take on the situation, speaking of helping with research as being part of a '*life cycle, do good, and you'll get good,*' conveying a moral responsibility akin to reciprocity.

For some individuals, an awareness of the relatively small population of CF patients heightened their sense of moral responsibility to participate in clinical research. Consequently, some felt a more pressing responsibility where a trial was struggling to recruit or was specifically targeted at patients like them. Informants' motivation '*to give something back*' often also extended to the Hospital and the CF team managing their own or their child's care.

> *We'd do anything to help them back for everything they have done for us[...]I just wish I could do more, you know, we are just so grateful to them, they have just been fantastic […]* Mother (Amy 16y)

For some older adults, their sense of gratititude and moral responsibility to give something back appeared to be particularly keenly felt due to: the many years of treatment they had received; an awareness of the vast improvements in CF care and life expectancy, and awareness that other people with CF were not as fortunate as themselves, both in terms of longevity and level of disability.

> *I've been part of a CF clinic, as a paediatric and as an adult, for the best part of forty odd years, forty-five years. When I first started, it was very much children, but you didn't really see anybody over ten. As I've got older, hopefully, the people around me have got older but there are less and less of us every year, and I just feel a little bit that you've got to give something back. You know, I mean I've taken all the the care from people doing it before me, so I just feel a little bit of obligation that if I can help, then I will.* Tim (49y).

An individual's sense of moral responsibility was further complicated in the context of parents, who had to balance their own values with the needs of their child and their responsibility as a parent. Balancing these multiple factors had the potential to result in decisional conflicts for some parents. For instance, one parent questioned whether she had the balance right between taking the lead role in decision-making and her tendency to say '*yes, yes we will do that trial'* without always saying to her son *'what do you think'*.

> *I sort of maybe do it a bit wrong myself because I go, yes, yes, we will do that trial, we will do it, and I don't always say what do you think Peter, do you want to be put through that [...] because my heart would say, well yes you should take part, it's important we should, without stopping and thinking hang on, what has Peter got to go through. Really so I suppose I am pretty selfish that way because I want the cure, so we are going to do that trial [...]* Mother (Peter 12y)

This parent viewed this tendency to say yes to trials as being driven by both a sense of moral responsibility to help other families with CF and her desire to find a cure for CF, motivations which she positioned as being *'pretty selfish'*.

7.1.3 A moral education

For some adults, their sense of moral responsibility to engage with clinical research had begun with a kind of 'moral education' from their parents that mirrored a process of enculturation to clinical research. They recalled how as children they were made aware of the personal and social significance of taking part in clinical trials.

> *My mum said, Kate, you know, they wouldn't, you know all these things wouldn't exist if people weren't prepared to take part […]* Kate (29y)

My mum just encouraged that you know obviously if you didn't do these kind of things then you know, if no one ever did them, no one would get any benefit out of them. […] John (33y)

These adults acknowledged how this powerful moral message had '*stuck with them'* ever since childhood and influenced their attitude and subsequent participation in many trials and studies. In contrast to this early introduction to the necessity of research, other adult informants reflected on how their parents had shouldered the *'worry'* of CF while they were younger. Now as adults their sense of moral responsibility to help with research was more keenly felt.

I never really considered CF as an issue because my mum and dad did all the worrying for me. So as soon as I become an adult and had responsibilities that I was like, a) felt that I had responsibility to other people to try and push my own treatment forward but also decided that I was, I wanted to be involved in trials […]. Alex (29y)

Resembling the moral education adults described receiving from their parents, parents within this sample also spoke about a moral training they either had begun or that they anticipated they would begin when their child was old enough. Parents described how this education would involve guiding and preparing their child about the value of participating in research which they equated to promoting *'good morals'*.

If you can almost sell it to your child as in, you know, tell them that they're doing a really good thing, then it can promote their sense of wellbeing as well when they're older [...] I'm looking quite ahead in the future, but it's teaching them about

responsibility as a citizen and about helping others out and promoting good morals in them as well. Mother (Harry 1y)

I would encourage her to take part in anything that is going to benefit, especially stuff I suppose that is still going to benefit her, that is I would encourage that even more, but even if it's not going to benefit her but will benefit others then I still think it's important. Mother (Alice 3y)

When this moral training would be initiated by parents was dependent on a number of factors including developmental stage, the value of a particular trial, personal belief system and the family dynamics. Prior to a child being ready to take on board the moral dimension of trial participation, parents spoke of the importance of *'quantifying*' and '*explaining* to the child what was *'going to happen'* in quite tangible terms. Particularly for children who were not yet teenagers, parents described extending research discussions to include a moral education, which was consistent with their own personal values and '*family set-up'.* For some parents, this began with a discussion about research in general, not connected to the specifics of a trial.

We have talked about it quite a lot about research in general because if we don't have research, then things don't get found out and things don't… they don't go on. So it has a knock-on effect for everyone and Rachael included.
Mother (Rachael 10y)

However, for some these discussions were only prompted by the specifics of a trial. In this situation, the value attached to certain trials appeared to be most influential in shaping the nature of the discussion. One parent described how the 'moral education' she provided for her daughter, to enable her to understand the value of participating in a fairly invasive trial, was something '*unfair for her age*' and

something she wished she '*didn't have to do this with my eight year old daughter'.* This parent indicated how she felt constrained by having to educate her daughter about the value of research in relation to her condition, due to this parent's belief in the promise and potential of this particular trial, which she viewed as being potentially '*huge*'.

> *When we went to the trial last year when she was eight and we had to talk to her a little bit more about CF because she had to have an understanding of the importance, because as soon as we said to her, "There will be blood tests," she was like, "No, I don't want to do it." So we had to try, without scaring her, we had to pitch it right where she understood that if she could consider doing this trial she'd be helping her and lots and lots of other people like her, she'd be part of doing something huge, first thing to correct a gene ever for CF [...]* Mother (Emily 9y)

In contrast, some parents described being selective about what they felt their child needed to know in order for them to accept the research offer as something reasonable.

> *I have told him, we are doing these trials to try and find a cure and if people don't step forward and do these trials there will not be a cure. So that is about as much as our Daniel needs to know to go… yes, all right yes. He doesn't need to go into specifics of what exactly like he knows he is having an inhaler, and he just thinks he is having an inhaler and he hopes it will make him a bit better kind of thing.*
> Mother (Daniel 11y)

Some parents spoke of negotiations with their child including a theoretical discussion about why research was needed and the aim of the trial, without going into the '*specifics'.* In contrast, other families spoke of being guided more by what

their child had initiated. For instance, one family spoke of how their daughter from a young age has always preferred to be talked to *'as an adult because that's the kind of person she is'.* Other parents assumed that living with a serious lifelong illness potentially resulted in children having to *'grow-up'* earlier than their healthy contemporaries because '*they're talked to by adults a lot more'* and ' *given more responsibility'.*

Conversely, some parents wanted to protect their children from the burden and responsibility of living with a lifelong condition, aiming to preserve a sense of '*normality'* for as long as they could. One parent spoke about how she was holding back information she thought he did not need to know yet, or did not feel comfortable with him knowing.

> *I relay it to Jack because I always kind of keep it all a little bit and even CF to a certain extent if it's not majorly affecting anything at the minute and for as long as I can keep it like that then I will do. Because I know what the ..... I can see over there, but we are not going there yet.* Mother (Jack 8y)

This parent stated she was not ready to '*go there yet'* implying she was not yet emotionally ready to consider the potential severity of her son's condition. This was supported by her acknowledgement that she had not '*ever said the word cystic fibrosis to'* her son until he was seven, when during his annual review he asked his mother '*why are we here*'. When they got home she:

> *'explained to him you have got something called cystic fibrosis, you know when you get poorly a lot, that is why you need extra medicines and occasionally you need IVs just to make you better, ok have you got any questions, and he just said 'oh I think it sucks' or something [...]* Mother (Jack 8y)

For some parents of children in the '*in between'* years, constructing fair involvement was perceived as *'hard for parents to pitch it right'*. This intricacy was in part related to the recognition that '*at the end of the day'* it was their responsibility to act in their child's best interests and make the '*right decision'*. Furthermore, parents' negotiations and their child's involvement were bounded by what parents wanted their child to know or the child needed to know about the '*seriousness'* of their condition.

7.1.4 'An inner glow' from contributing to a common good

Informants who had agreed to take part in clinical research viewed their participation as something virtuous, indicating that there was 'a *sense of fulfilment*', '*inner glow'* or *'feel good'* factor, from participating in something of value.

> *I can't say yes, I will lead a better life because of it, but it gives you a sense of fulfilment that you've done something that maybe somebody else can have a bit of advantage over. But it's not a personal thing; I haven't said, you know I'm not fussed that the advantage is for me.* Tim (49y)

> *I think you get a, an inner glow, however small, that you've taken part.*
> Francis (63y)

While an informant's motivation to contribute to a common good could be equated to a form of altruism, a 'feel good factor' derived from upholding a sense of moral responsibility comprised an important intrinsic or psychological pay-off. Consequently, informants' moral accounts of their decision to participate typically equated to being '*selfless to a point'*.

> *If people don't take part in these things and aren't willing to be selfless to a point, then it ain't going to advance, and you're not going to find the cures [...]* Adam (19y)

For example, Kate who had taken part in several clinical trials perceived her psychological motivation to '*feel good about myself*' by helping future generations as being partly *'selfish'*.

> *I feel like I owe it to all the people in the past that have done things that I have benefited from, so it's sort of like a payback you know and I know that I will be helping so it makes me feel good about myself because I know that I am helping future generations of people with CF, so it is quite a selfish thing I think.* Kate (29y)

I viewed informants' references to a *'selfish'* motivation as an acknowledgement of this intrinsic pay-off which they derived from contributing to something they regarded as both socially desirable and morally valuable.

> *If there is anything that you can do, just a little, little tiny, tiny little little thing that in 10 years time, because Jack and 3,000 other children have had this certain inhaler we know that it is going to help not just your child but kids that are being born now with CF, you can't not do it really I don't think.* Mother Jack (8y)

I viewed the number of people this parent hoped to help in the future as conferring the value of participating in a clinical trial and her corresponding sense of personal satisfaction from taking part. Similar to adult and parent accounts, some older children also implied that they derived a feel-good factor from contributing to something worthwhile. For instance, Rachael's father directly reinforced the value of her current participation in a nebulised drug trial and Rachael requested this section of the interview be included here.

Father (Rachael 10y): *But with Rachael's doing this inhaler for 20 seconds a day which is basically is all it is, we don't know how many people it's going to help at the end of the day, so for 20 seconds a day, you don't know how many people you are helping, Rachael.You could be helping thousands just doing that, not just you… do it for yourself.*
Rachael: *Can you put this bit in it?*
Emma*: Yes I will put this bit in.*

Clare, who had been approached to take part in two clinical trials, described taking part as both helping herself and *'millions'* of other people.

I like the fact that they have done, that they do the trials and because it makes me think that you know I can provide answers for other patients with cystic fibrosis and that I am not just helping myself it's helping millions of other people as well.
Clare (17y)

Again, the number of people Clare hoped to help appeared to confer the value she assigned to trial participation and her personal satisfaction at being part of something worthwhile. Some parents and children also described feeling '*quite lucky'* or '*honoured*' to have been invited to take part in clinical trials.

We feel quite lucky that we've taken part. I think it's important to then think in Dylan's growing up that he was important in finding out something quite vital to the functioning of, treating quite a common [infection], well for CF people, and how the NHS deals with it. Mother (Dylan 2y)

I was particularly; I was quite honoured that they'd thought of us [...] I felt quite proud of Emily that we'd been approached, to be honest. Mother (Emily 9y)

Consequently, informants' accounts conveyed interdependence between the value they placed on research and the intrinsic pay-off or feel-good factor they derived from participating. Moreover, the greater value individuals placed on research, the more emphasis they placed on their moral responsibility to participate in research.

7.1.5 Making sense of saying no: balancing personal interests and responsibility:

In a context where informants positioned research as a valuable activity, to which they ascribed some sense of moral responsibility to participate, guilt could arise when an individual felt it was in their child's or their own best interests to decline participation.

> *I did feel guilty, and I did say, "We would do anything for Emily and anything for the CF community, we did the London trial, but this particular time we have to opt out because we want to do what we feel is right for Emily right now", and that's why we declined it* [TORPEDO-CF] *[...]* Mother (Emily 9y)

> *Part of me felt guilty for saying no, but it was Mia's interest for me that, we wanted it, we wanted it rid, rid of it didn't we.* Father (Mia 8y)

In this situtaion, an individual often employed a guilt discourse to make sense of their discomfort at turning down something they believed to be morally valuable. I interpreted these references to guilt as an indication that these individuals acknowledged the moral value of trial participation yet this had to be balanced against their other responsibilities and their personal interests. How individuals made sense of their participation decision was typically multi-dimensional involving a series of trade-offs extending beyond a moral discourse. For parents their role of acting in the '*best interests'* of their child was central to their decision,

and this often superseded their moral responsibility to take part. Nevertheless they often employed a guilt discourse to make sense of turning down something they felt they had a moral responsibility to be part off. This discourse was most prominent in individuals who had emphasised the moral responsibility they felt towards participating in clinical research, and often it was parents who did so rather than patients. Indeed some parents conveyed their responsibility to participate as feeling almost obligatory. Consequently avoiding an anticipated feeling of guilt was an important motivation in their decision to allow their child to participate in clinical research.

> *I did initially feel a bit obliged to say yes [...] it's just, you know you don't like to say no to people, and it was in the back of my mind worrying about side effect and things like that. But then after thinking you know going along the lines again if nobody does anything, nothing will change, and treatment will always be the same, and nothing will get advanced.* Mother (Nathan 16y)

Teenagers and adults also conveyed a sense of moral responsibility to contribute to something that they believed to be of value that had the potential to improve the lives of people with CF in the future. Therefore, their decisions to decline also resulted in a moral *'wrestling'* and a sense of feeling '*guilty*'. Adults who had conveyed a more reticent or ambivalent attitude towards research equally expressed a moral responsibility that they *'should take part'* to help themselves and others. One informant countered this sense of responsibility by imagining '*loads*' of other people willing to take part or that an alternative method of conducting the research existed if nobody volunteered.

> *I just don't volunteer because I'm sure there's loads of other people that are out there probably would volunteer over me [...] I'm sure if I don't take part there'll still be another way for them to do the research[…]* Sara (30y)

Some informants worked hard to morally defend their decision to decline a particular study in relation to other studies that they had already participated in. Several informants indicated that they had taken part in this study to compensate for the trials or studies they had turned down in the past.

Informants indicated that there was no external pressure surrounding trial participation decisions by stating that the CF team *'were quite happy if I said no'* and that '*nobody made them feel like that'*. Hence, it seemed that their sense of guilt was personally derived, a view that '*you can't expect everybody else to find the information'* or '*to do the work'*. Some informants also expressed concern about what *'other people might think'* or the personal discomfort of having *'to say no to people'*.

It is possible that references to guilt were employed as a performative device to enable informants to present themselves as a good person, even though they had said no to something they believed to be a virtuous act. It is equally possible that references to guilt represented intrinsic cognitive discomfort or 'cognitive dissonance' (Festinger 1957)[12], which resulted from the difficult situation of trying to balance an individual's moral integrity and self- interests. Consequently, these accounts highlighted the tension between what is theoretically '*something good'* and

[12] Cognitive dissonance refers to an emotional state which occurs when an individual holds attitudes, beliefs or behaviours, which are not consistent and are in disharmony (dissonance) (Gawronski & Brannon, 2016; Festinger, 1957)

a personal reticence about what may be involved at an individual level in a context of uncertainty.

7.2 Patients' and parents' perspectives: a psychological discourse

7.2.1 'Hoping for the best'

A moral responsibility to contribute to the continued research effort in cystic fibrosis was an important foundation of a fair research offer, yet always threaded through this moral discourse were various strands of hope.

Personal expressions of hope were emphasised where individuals had agreed to participate, and were less prominent in informants' accounts of trials that had been declined. In the first instance, as discussed in the rational discourse, individuals, who had consented, indicated how they '*hoped for the best*' while accepting that there were no guarantees.

> Mother (Rachael 10y): *I think that people have to make sure that they realise that it's not going to make an effect sometimes […]*
> **Father: *It's just, something she does, every day.***
> Rachael: *Just hope for the best.*

> *When we were discussing it* [the TORPEDO-CF trial] *at the hospital we said you know it's not going to be detrimental to Alice's health but it's not going to improve her health going on it necessarily, but like they said if they can know from this trial in a few years time whether it's better to get them in for IVs then that will affect her in the long term and if they find that it is more effective, that they have IVs then that is good because it means they will have to work at getting them in quicker […]*
> Mother (Alice 3y)

A hope for the best personal outcome typically included an acceptance of the broader future aims of the research. Furthermore a personal motivation to help '*other people'* as well as themselves, or their child, appeared inseparable from a personal sense of hope. However, no account of their decision to participate in clinical research was solely based on the *'bigger picture'* or common good.

> *I just see it as a benefit for everybody really, for everyone with CF not just, not just for Isabel.* Mother (Isabel 1y)

In the context of physically demanding novel trials such as early phase gene therapy, personal motivations and conceptions of hope appeared even more involved. These informants described how they held onto a hope for personal benefit, despite being fully aware that this was unlikely and not the objective of the trial. Nonetheless, this improbable hope and a physically demanding time-consuming trial were buoyed up with a combination of other personal motivations in addition to contributing to the '*bigger picture'.* For instance, these informants described the psychological satisfaction derived from of being part of something '*revolutionary'* that may add up to finding a cure for CF.

> ***What were the important factors in deciding to go to the next stage?***
>
> *Self-gain partly, […] because this was a safety trial I knew that I was definitely going to get a dosage of gene therapy and I knew it wasn't going to do much because it's just one dose, but just to say that yes I know I have had a dose of gene therapy and it just sounds ridiculous doesn't it but just to have that experience and to say I was part of it and I had yes that was my main motivation[…] To be able to say oh I was part of helping find a cure for CF; I think that is the biggest ego thing you can ask for definitely*. Kate (29y)

> *I guess a little bit of me thought well maybe I will get a small benefit. I just found it, personally I found it fascinating, like antibiotics trials, I would happily get involved with them, but they are not like, you know antibiotics have been around a long time it's nothing revolutionary, but for me, the idea of trying to treat someone at a genetic level, like at the very building blocks of any person like you know that's kind of, that's science fiction really and just to be part of it. Whether it did anything or not just to, that people are even attempting that was quite exciting to go and see.* Alex (29y)

I viewed these acknowledgements of small hopes for personal benefit as not based on misunderstanding or misconception, but as informed individuals actively choosing to hold on to the possibility of self-gain and a position of optimism. Furthermore, the psychological benefits emphasised within these accounts were present to counter any disappointment and helped sustain their motivation, however small.

For the most part, individuals perceived an awareness that research is on-going, aimed at trying to improve treatments, as something potentially reassuring and something that served as a '*confidence-booster'* and source of hope for some individuals.

> *I think it is quite important for some trials to be advertised. I know that research is happening in general , you know sometimes you can think well what is actually happening out there, how we are progressing forward, so I think from that point of view it's great, it does give people hope [...]* Megan (26y)

Patients, or parents, who had declined all offers to participate in research described being happy to be approached, perceiving the process as something constructive, '*they're trying'*, and the approaches don't do *'any harm'*. In fact, most patients and parents valued being offered the choice to participate in research and perceived being approached as being '*kept in the loop'* and avoiding '*missing out'* or being '*left out'*.

How individuals negotiated hope was central to their view of a fair offer. A more far-reaching concept of hope was much less prominent in the accounts of individuals who had declined most research invitations and individuals who appeared more reticent about engaging with research. For instance, Sara had declined several trials due to a lack of *'appeal'* or interest and her concern about taking time out of work. While she viewed research as essentially '*helping'* her account did not convey an optimistic view of the promise of clinical research, and she failed to see the direct impact of research on her life at the moment. For individuals that had turned down a research invitation, the costs associated with participation had been viewed as outweighing any anticipated hope for personal benefit.

7.2.2 'Keeping our spirits up': hope as coping

While many informants conveyed a hopeful attitude that research will lead to future improvements, for some informants actively engaging with research was positioned as an important '*way of coping with the whole CF thing'* because *'the truth of it is, in the end, it's going to lead to death'*.

> *The fact that you are taking part, it's a bit of optimism a bit of light at the end of this tunnel kind of thing. Do you know a bit of positivity because it's a very negative*

thing … there is nothing positive about it whatsoever, so any little bit of positiveness you can get out of it, just makes your day that bit more, come on… let's keep going, keep going, just keep plugging away and see what happens. Mother (Jack 8y)

Participating in clinical research was conveyed as something positive to counter the negativity connected to this '*ongoing, life-threatening'* condition. Accounts illustrated 'a *bit of optimism'* and something to '*keep your spirits up'* combined with the tangible act of engaging in something worthwhile, comprised interrelated sources of hope. This sense of empowerment derived from a hopeful outlook and active engagement was present across subgroups, it was most prominent in parents' accounts and the least prominent in children's.

Throughout their narrative, parents called attention to the immense psychological impact and the '*overwhelmingness*' of caring for a child with CF. Correspondingly, their engagement with clinical research was positioned as providing an important aspect of their emotional defence to this demanding responsibility. One parent had described how she had created a '*hope board'* as a way to cope with her daughters' diagnosis. She described how she had *'cut printed things out, positive things, and stuck them all on this card'.* A novel mutation-specific clinical trial considered the nearest thing to a cure, was viewed as the most *'positive thing'* on her board. Engaging with research was considered by parents as an important coping strategy, to counter their distress, and provide them with a sense of control, *'taking something positive'* from their child's illness, which they viewed as an '*awful disease'*.

7.2.3. 'Pinning hopes on a cure'

Informants' perceptions of hope were complicated by the public perception of the curative scientific function of research. Moreover, a hope for a cure was particularly

heightened in the context of CF care, due to CF being the first gene for a human disease to be discovered and hence the first condition to offer the promise of gene therapy (Riordan et al., 1989; Kerem et al, 1989). For some informants, the identification of the '*genetic code*' for CF and the expectation of related curative treatments provided a tangible basis for their sense of hope.

> *When she was diagnosed, and I was thinking oh my God no, there is just no hope, and then [...] the genetic code was unblocked or recognised, or whatever the word is and then it was, you know, it was like a speeding train really [...] Well once that was done that's when all the possibilities became real.* Mother (Amy 16y)

Adult informants remembered the excitement expressed by their parents around the possibility of a cure following the discovery of '*the CF gene*'.

> *I would have been 7 when the CF gene was discovered, and I remember my parents being really excited like, you know oh a cure must be round the corner [...]*
> Kate (29y)

For many informants, a sense of hope gained from an expectation of treatment progression through research was inseparable from a hope for a cure.

> *We're desperate for a cure, and if nobody does research then they will never find a cure, so I think that's the main driving thing to it really.* Mother (Daniel 11y)

> *As parents, the only hope you have is for a cure, and without research, without clinical trials, they'll never be a cure.* Mother (Dylan 2y)

To do with CF, it's obviously always working towards a cure, and any research is good research [...] Luke (22y)

For these informants, treatments with a curative potential were an optimistic prospect providing the impetus for their engagement with research and influencing their receptivity to clinical trials and clinical research per se.

Within the child sample, only older teenagers directly spoke about the curative potential of clinical research.

It's a good thing, definitely, because it means that people like myself we can have more advanced treatment, in the long run, you know and eventually maybe find a cure or things that will prevent us getting more infections [...] Clare (17y)

One teenager and her mother during a joint interview described holding on to the possibility of a cure as a '*lifeline*' and something that '*gives us hope'*. At times during their narrative, they implied their hopeful attitude might be idealistic, but this concern was countered by the significance they attributed to the therapeutic value of holding on to this level of optimism. A similar sentiment was echoed within other accounts.

Mother (Amy16y): *About 15 years ago I first was aware of the possibility of gene therapy, but it was so far away then and...*
Amy: ***And now it's so close.***
Mother: *And now it is so close. We have just got to keep her well enough; you know until it comes, and well always of course*
Amy***: Always, but just something to work towards, keep yourself well, sort of a goal.***

Mother*: I know Amy ... yes exactly it is absolutely, well it's a lifeline.*
Amy: *It is.*
Mother: *It is such a positive thought because when Amy was diagnosed there weren't really, well there is no cure now at the moment, and that is the nearest thing in Amy's lifetime that there is going to be to a cure and we call it the cure don't we?*
Amy: *It will be, won't it for me.*

Furthermore, this family indicated their sense of hope derived from the curative potential of future treatments had provided an incentive or *'goal'* to work towards, facilitating adherence to '*relentless'* treatment regimes which could *'drive you mad'*. This parent described how, like other teenagers within this sample, her daughter had experienced a period of non-compliance during her early adolescence which had resulted in a significant deterioration in health and reduction in lung function.

<u>If you want to stand a chance</u> and you know Amy is 17 on Friday, <u>so you know if you do it, you will keep well you know, and all the lovely new stuff coming along</u>.
Mother (Amy 16y)

A notable shift in focus occurred during the interview, from disclosure to direct dialogue with Amy (underlined section in the quote) which served to accentuate the significance this parent placed on her daughters continued adherence to her treatment regime, to stay as well as she could for whatever the future might hold.

Often united with an individual's personal sense of hope attached to the promise of new therapies, was unease regarding fair access to the potential benefits of these ongoing and upcoming novel trials. Some informants conveyed a sense of

'unfairness' and disappointment at the inequity of opportunity to take part in innovative trials such as the *'gene therapy trial'*, due to being in the '*wrong area'*.

> *In terms of the gene therapy trials, it is a bit frustrating that just because I don't live in London, I can't take part in them. So it does seem unfair sometimes that you are limited by where you live but I guess that really can't be helped and when they do a bigger study ,you like to think that everyone will have the accessibility to take part in it […]* Molly (24y)

For some adult informants who had witnessed first-hand the high expectations and the unrealised promise of gene therapy their accounts typically conveyed a more cautious attitude towards the promise of a cure. Several adults who had '*pinned their hopes'* on a cure being '*round the corner'*, acknowledged how this had resulted in disappointment and an ambivalent attitude towards clinical trials and their engagement with research.

> *I don't look at it too deeply, because the only reason why I say that is because I looked at this article quite a few years ago now, and they were like, oh, we're going to find a cure in five years, and that's stuck with me, and it's like, and I don't feel very close [...]I don't read too much into research at the minute, because I think you, it builds up your hopes a little bit and I think people can read into it too much.*
> Joanne (23y)

> *I really don't know what's going on out there for research. Obviously, gene therapy that's one thing, but I really don't know what's going on if I'm honest. I try and avoid reading up on it because I feel, if I read up on it, it's always disappointment.*
> Sara (30y)

While these informants still accepted research as valuable, overly optimistic claims of research had reduced their sense of hope derived from the expectations of research. Their accounts illustrated the '*flipside*' to hope, wherein disappointment or disillusionment had the potential to act as a deterrent to their commitment to research.

Other informants, while disappointed by the slower than hoped for progress of gene therapy, also recognised the personal significance of wishful thinking with regards to the promise of future treatments. Consequently, many informants occupied a middle ground, in which they embraced the optimism of scientific ambition but had tempered their expectations about the possibility of a cure in line with current evidence.

> *These trials they are doing at the moment for this gene therapy where they are hoping to find a cure for CF[...] it's just hearsay at the moment I think more so than anything it's just people wishing that that is going to be.* Mother (Isabel 2y).

These individuals accepted that a cure was unlikely to be realised in their own or their child's lifetime, yet it still provided an effective motivational resource for their engagement with research and managing their life with CF. However, some individuals expressed concern regarding the continued focus on the prospect of a cure, despite the lack of results, both in terms of psychological impact of unrealistic hope and the allocation of research resources.

Concern was expressed that this type of research soaked up vast amounts of money, leading to the neglect of other important areas of research which had the potential to improve the lives of people with CF that are already here.

It's kind of going down the wrong track, they haven't got it right yet, and they keep pumping out for money and I think the thing with the CF trust, that I get annoyed about with the trials is, they have really, obviously they have spent a lot of money on the gene therapy trials, but they kind of put all the money to that pot so research on other areas which is really important for CF care, they have kind of let go by, so like the nutrition, the digestive side, stuff on diabetes, there is not enough research on there, so it's more kind of find a cure but forgetting about the people that are already here. Laura (24y)

Some individuals advocated for a more honest dialogue, expressing concern that '*talk about a cure'* may be both enticing and responsible for fuelling '*false hope*'. They spoke of the importance of being '*realistic'* about the low likelihood of a cure for CF in their life-time - though they also recognised that this might impact on some people's receptivity to clinical research.

7.3 Practitioners' perspectives: a psycho-moral discourse

7.3.1 Research as a common good

Consistent with the perspectives of patients and families, the foundation of a practitioner's view of a fair research offer, rested on their acceptance of clinical research as a common good, necessary to ensure the improvement of clinical treatments. Reflecting over long-standing professional careers, practitioners identified improvements in practice as being related to new knowledge gained through research. They also acknowledged that advancements in medical knowledge were dependent on willing '*people taking part in trials'*

The whole of medicine depends on people taking part in trials, in order to advance knowledge [...] Doctor 12 (adult)

I think that research is vital if we are going to be improving our care as the years go by […] Doctor 1 (child)

Paediatric practitioners drew upon the exemplary success of treatments for acute lymphoblastic leukaemia (ALL) achieved through paediatric oncology trials to validate their belief in the value of clinical trials.

The only way that we are going to get better treatments is by doing research and you know I think the best study, the best example of studies, for early oncology studies you know, ALL where you know treatments got much, much better and that's only through every patient being entered into clinical trials, and I think that's the way forward for the rest of medicine. Doctor 9 (child)

In contrast, adult CF practitioners were more inclined to draw on the success achieved through research within the specialty of CF, now no longer considered a condition of childhood, to underpin their belief in clinical trials.

Cystic fibrosis for me embodies the way medicine should go with research, because in the eighties, it was a bit 'the poor dying children', we've just got to do whatever we can because they're going to die'. So, people would do amazing, you know you'd throw a treatment at them with no evidence whatsoever, and it was well meaning, but it never got us anywhere. So I've seen the change of saying.....no, okay there are limited numbers but you can do trials and you can sort out what's best and let's move it forward, and you know, huge advances [...] Doctor 6 (adult)

While practitioners conveyed an acceptance of the research endeavour as a common good, necessary to uphold the progress narrative of modern medicine, they also recognised how both practitioners' and patients' views on clinical research were variable and dependent on experiences and awareness. For instance, several practitioners reflected how at times they *'sensed'* patients' levels of trust and receptivity to research in some ways mirrored the ebb and flow of research scandals in the media.

> *I think it's slightly harder well, it is definitely harder than it was twenty years ago, but things like Alder Hey and, and Northwick Park, and Bristol Children's and things like that, started people asking more questions. But that's eased off a bit in the last few years […] and you get a feeling that people are keener again to participate in trials.* Doctor 3 (child)

Practitioners also acknowledged that their views on research had changed over time according to experience. With several reflecting on times when they had felt more negatively towards research.

> *If you want progress, you have to do research. It's not just something horrible that you have to do because it looks well on your CV or something like that anymore, but it is really something where you go, "Well, actually in the long-run this is the only way how we can move survival and patient quality of life in CF care forward if we do proper controlled research .* Doctor 4 (child)

Other practitioners spoke of how they had witnessed other professionals' reluctance to engage with research, viewing research as an '*obstacle in the way of clinic'* due to lack of awareness and understanding of '*the benefits of it'.* Suggesting research may be misunderstood and consequently undervalued or avoided by some practitioners.

7. 3.2 Why be a recruiter: balancing responsibility and personal interest

Resembling patient and parent accounts, practitioners also constructed a moral dimension to their engagement with research. Practitioners'accounts conveyed an interrelated professional and moral sense of responsibility to engage in research, as failing to do so may result in giving treatments that aren't *'actually good'*.

> *I can certainly look back in my career and think about how things have evolved, why they have changed […] some of the things that we used to do that we don't do anymore because we know through research and studies that they weren't actually good […] if we don't do any research then we are not going to change are we and we are not going to improve.* Nurse 6 (adult)

Improvements in treatments, derived from the '*worthwhile*' endeavour of clinical research was identified by most practitioners as a key motivation towards their engagement with clinical research.

> *What drew me to research was really that possibly you can improve things for people and make a difference [...]* Nurse 4 (child)

> *I am very interested in research, and I want my patients to have a better treatment that is the ultimate thing [...]* Doctor 2 (adult)

Nevertheless, consistent with patient and parent accounts an underlying belief in a contribution to a common good, alone was not enough to sustain a practitioner's engagement with research. Practitioners acknowledged a personal expectation or '*need to get something out of*' their engagement with research. Personal interests were varied and typically included a number interrelated personal *'drivers'* or

'motivations' which included such things as: '*interest*' *'something different'* *'money'* and *'personal, academic development'*. Without these expectations being met, practitioners indicated that the role of recruitment may be viewed as another '*chore'* amidst more pressing clinical responsibilities and that '*altruism'* alone was not enough to counter this tension. Practitioners viewed altruistic motivation as equivalent to contributing to generalized aims of research or what I have referred to as a common good. Comparable to patients and families, practitioners were unlikely to take on extra tasks solely for the common good, for little or no personal return.

> *The sort of expectation that everybody does research is daft really because they need to get something out of it, I think […] The incentive is not great, other than altruism, and when you're really busy, altruism sometimes plays second fiddle to everything else.* Doctor 3 (child)

Practitioners also spoke of a professional requirement to engage in clinical research, and some described feeling a degree of pressure from fellow professionals to be involved in research at certain times during their career.

Time was also typically viewed by practitioners as something which was in short supply and a constraint to engaging with research activities. How clearly practitioners' research responsibilities were demarcated within their professional role, determined how reasonable they perceived there research responsibility to be. Consequently, for a practitioner whose position was research-based such as the role of 'research nurse', time as a constraint did not feature in their accounts. However, for those without clear research roles, time for research was constrained leading to conflicting priorities and a sense of tension concerning research duties while also managing excess clinical responsibilities.

> *It's time consuming when you haven't got time in your week dedicated to doing research then you are having to fit it in, amongst other things and it makes it hard [...]* Doctor 12 (adult)

Practitioners whose salary was not dependent on research implied that it was a reasonable assumption that research would take a lower priority than clinical commitments.

> *If you are a senior lecturer or a clinical lecturer or a clinical scientist, your life does depend on research, you know you have got to be publishing the papers to justify your salary [...]* Doctor 5 (child)

Even where practitioners had some form of '*protected time*' for research related tasks, they pointed out that in reality, this time was inadequate or not truly protected in the demanding clinical environment where practitioners viewed their patients clinical needs as being '*paramount'*. However, practitioners spoke of time for research as a flexible resource, which could expand or contract depending on the perceived fairness of the situation. In situations where personal interests, professional responsibility and the value of the trial outweighed additional commitments of research, practitioners indicated that time was found. Nonetheless, they accepted that time could only be stretched so far and even where studies were considered to be worthwhile, additional resources may be necessary to buy more time to meet the demands of recruitment.

7.3.3 'The morality of the study'

In addition to a moral and professional responsibility to contribute to the research endeavour, practitioners also spoke of their responsibility to ensure the worth of

individual studies. This involved personal judgements centred on '*the morality of the study'*, that is to say, whether practitioners viewed the research to be '*decent and meaningful'*. Despite all the clinical research being described as having passed the ethical scrutiny of a committee review, they spoke of the additional moral judgements they made about the worthiness of each individual study or trial. Practitioners indicated that they would be reluctant to be involved in or '*ask anybody to participate in a study'* they '*didn't think was appropriate and of good quality'.*

> *I would like to know that, I would like to believe that I felt that this was the right thing to do. It goes back to the morality of the actual study I suppose.*
> Doctor 1 (child)

> *First perception is whether you really believe in the study for which you are recruiting, which I think makes a difference [...] you need to sort of believe that this is going to help* Doctor 11 (child)

Other motifs of '*the morality of a study*' included a hypothesis which they could *'embrace'* and a trial design they understood and agreed with.

> *When you think about taking part in a study you have to, embrace the hypothesis of the study because if it's not one with which you agree, then I think ethically you wouldn't want to, you just couldn't participate. So it's a question that you have to believe is a genuine question, and with a trial design that you would be happy to put your patients forward for.* Doctor 10 (child)

Some practitioners identified *'sufficient funds and resources'* as being integral to research of value and something which needed to be guaranteed before accepting a study. Others were ambivalent about the '*lucrative*' nature of some commercial

trials, particularly if they felt the study design was questionable. One practitioner recollected how during a time at a GP practice, she had struggled with the morality and fairness of '*a double blind placebo'* asthma trial, which ultimately, she avoided referring potential participants to. She described the trial as primarily a *'money making venture'* which potentially involved leaving a symptomatic child, with no preventative treatment. Now as a CF practitioner, while she accepted the need for clinical trials, she did not want to be placed in such a position again, where her primary role to care for patients was being compromised by research responsibilities which she believed diverged from this role.

> *I wouldn't like to be put in that position that I was put in when I worked in general practice. And I think if anything, that really I think over exposed me to that and put me off [...] So then when somebody says oh about some research you sort of almost like, you go into shut down and you sort of fold your ears in and think I don't really want to like get involved with this because I am busy looking after my patients because that is what we do.* Nurse 6 (adult)

Practitioners also indicated how shifting economic and political influences on the research *'industry'* had the potential to influence their perceptions surrounding the morality of particular studies. For instance, one practitioner conveyed an obligation to participate in commercial studies to accumulate the economic resources to facilitate research in line with his personal interests.

> *I don't do commercial studies because I love commercial studies; so, in the past, I did them because they raised money that allowed me to do the research I wanted to do. And I do them now because I have to do them to be seen to be contributing to the Trust's research effort and income, so that I can get time in my job description to do*

research in which I can then go and get money to do the stuff I want to do which is non-commercial stuff […] The money flows from recruitment.
Doctor 3 (child)

7.3.4 Making sense of recruitment: the morality of marketing

Practitioners engaged in a moral and psychological deliberation to formulate their role in the process of recruitment, a role that they recognised as requiring a different '*balance'* to routine clinical consultations. Their accounts also illustrated how they dealt with the significant '*change in focus'* which occurs in the clinical relationship during trial recruitment, which involves asking patients to '*put themselves out'* or to do something extra to their necessary treatment.

Many practitioners viewed recruitment as '*ultimately their responsibility'* to ensure eligible patients are offered the *'choice'* or *'option'* to participate in a trial.

Every family has their own nuances, and they are you know there are always difficulties of one form or another. I think that one has to at least let the families know about the trial and then, give them the choice. Doctor 10 (child)

It is an important as part of a patients' journey and their treatment, giving them the choices. Nurse 2 (adult)

Some practitioners moved away from a more neutral framing of recruitment as an option or choice to the more positive framing of recruitment as offering an '*opportunity*' for patients to try new drugs coming on to the market or a *'chance they deserve*'.

You certainly give everybody a chance because if they were actually eligible and the right criteria then that's...their decision, not mine and the fact is that they deserve the chance to know about it. Nurse 6 (adult)

I never apologise for introducing the possibility of being in a research study. To me, it's an opportunity for a person with CF to kind of get the access to a new treatment. Having said that, you always have to be aware when you're doing studies; it may not always be doing good and [...] look we appreciate all the effort you put in, in these trials and some of them aren't going to show a benefit, that's why we do a trial. Doctor 6 (adult)

Some practitioners used a marketing discourse to denote this shift in position from one in which they are offering something the patient '*needs'* or that is the '*right thing to do'* for that patient, to one in which they were no longer in this position, but rather they are offering something that is primarily to inform future knowledge. From this position, the practitioner viewed themselves as a type of *'salesman'* with a particular '*product to sell'* and a '*pitch'* or *'patter'* to be '*prepared'* and '*fine-tuned*'.

It's like a salesman; it's difficult to sell a product if you don't believe in it [...] You need to know your study, you need to understand what you're talking about, because you've got to be able to sell your product very positively and confidently, and knowledgably. Nurse 3 (child)

I would have to do the looking into it [...] so that I knew exactly what I was doing and what it was about and believe in it really so that you can sell it. Nurse 2 (adult)

Equivalent to the preconceptions of a reputable salesman these accounts conveyed a requirement to believe in your product, which links back to the '*morality of a study'*

discussed previously. However, the standard assertive persuasive techniques that are often associated with business were reconciled with the requirements of informed consent by practitioners advocating a form of '*unbiased clinical marketing'* or 'fair marketing'.

> *Its sort of a clinical marketing, research marketing, without being biased but just saying, you know your child may be able to be included in this study, would you like to know more about it.* Doctor 1 (child)

Practitioner accounts illustrated how 'fair marketing' involved both a '*difficult'* and *'different balance'* requiring a *'positive and neutral*' position.

> *You need to keep a different balance, just because you believe in something you can't just force or talk more about the positive things of the study, when you are approaching the parents, that sometimes can be a bit subjective[...]and I think it can be a bit difficult, we are all human beings [...]* Doctor 11 (child)

This is a position which was open to personal interpretation, requiring a balance that was viewed as being hard to maintain. The concept of remaining positive and neutral was captured by this practitioner's illustration of how he might convey a study to a potential participant.

> *I will indicate that this study is one that we support and the study is one that we, it's a genuine question that we genuinely want to answer so that if they feel able to participate then, that would be very helpful. But also if they wish not to participate then, then I am not going to think any worse of them, and the team will still care for them.* Doctor 10 (child)

This balance was even more difficult for those practitioners who felt the *'pressure of numbers'*.

> *There's a pressure on us for recruitment, no doubt. The companies always have deadlines, and I suspect that we are a bit more pressured than perhaps we'd like [...]*
> Doctor 6 (adult)

Practitioners spoke about *'onerous numbers'*, achieving '*targets'* or upholding recruitment, reputations and some emphasised the scientific, personal and economic requirement of achieving recruitment targets more than others. Those practitioners who were able to distance themselves from this pressure were less '*stressed by it'* or '*worried if people say no'*.

The practitioners' discourse on unbiased marketing also moved into the realm of advocating research participation as a common good and something morally commendable. Practitioners spoke of providing a '*convincing argument'* about why a trial is needed whilst emphasising the generalised aims of research whereby '*people are actually helping the community'*, rather than themselves.

> *Many families are happy to help if you know you can make a convincing argument that knowing this would you know further science and could help other children.*
> Doctor 8 (child)

One practitioner compared recruitment to an act of inviting individuals to act altruistically *'to do their bit just like blood donoring'*.

If you look at reported reasons for taking part in research, altruism and wanting to improve things comes out top, top of the list most of the time. And so there is, I think, a greater perception of doing their bit just like blood donoring and giving blood, and things like that, than we give the public credit for it, I think [...] as long as they're not going to come to harm, and it's not going to be totally, all-consuming, they'll do it and they'll volunteer to do their bit in the majority of cases
Doctor 3 (child)

Viewing trial participation as a morally commendable action some practitioners were inclined to regard the process of recruitment as akin to asking '*a favour*' as opposed to selling a product.

I always think it's the patients doing us the favour that they go through this and they do it for us and for themselves, but I always say to them, "You're doing me a favour, or you're doing us a favour if you're doing that. You need to be aware of that. You could just sit in your chair and wait until the drug's ready in two years' time and then just take the benefits from other people being in the trial. So I'm very grateful that you're doing us this favour." I can't forget that. That it's them giving up their time and their efforts and everything. Doctor 4 (child)

In the context of trials with little, or no, potential therapeutic benefit, positioning recruitment as comparable to asking for a favour could be seen as ethically preferable, compared to instilling or perpetuating unrealistic hope or expectation of potential individual therapeutic benefits. Nonetheless, viewing recruitment as akin to *'doing a great favour'* brought into view the reciprocal nature of the favour and potential sense of obligation or indebtedness. Practitioners recognised that particular individuals might feel concerned about letting people down or being

treated differently if they declined a trial. A view which may be more keenly felt in a long-standing clinical relationship.

> *You have to be careful of, people... some people take the view, I'm letting you down if I don't do this trial for you, and you've got to be careful of pushing people when they really don't want to.* Doctor 6 (adult)

Stressing or even over stressing the voluntary nature of the proposition was considered an integral component to the fair marketing of research. Indeed, one practitioner inferred that he had found that emphasising the voluntary nature was not only at the heart of a fair offer but also proved to be an effective marketing strategy of its own.

> *I always tell people who start working with me, is the key thing is not to be pushy[...] The more you almost put them off, the more comfortable they feel [...]And the more you give them an option to get out, the less likely they are, is my experience.* Doctor 3 (child)

However, some practitioners recognised the difficulty in ensuring that there is no pressure, whilst also conveying the value of participating in a trial.

> *They need to know there is absolutely no obligation or pressure and it's difficult because you don't want to put everybody off, well if there is no pressure I won't do it [...]* Doctor 5 (child)

In order to make sense of recruitment, practitioners had to balance their belief in the morality of the trial while approaching patients in the 'right way'. How

practitioners constructed the 'right way' was nuanced according to their personal values and their conception of the value of the trial.

7.3.5 A fair selection

Some practitioners emphasised a moral responsibility to try to avoid being *'selective'* due to prior knowledge of patients and to aim to approach potential participants '*fairly and squarely*'. Several practitioners' accounts resonated with the findings from the patients and families accounts, with a view that patients want to know about trials and valued being asked.

> *We try not to be selective in terms of personality or whatever; we go down our, we've got our patient list [...] I am coming to believe that people want to know about the trials. If they're eligible, give them the choice [...] in general I think there is little harm in the information that a trial's going on. Occasionally, patients benefit from the 'oh they thought of asking me'.* Doctor 6 (adult)

While practitioners implied a moral responsibility of fair selection, they also indicated this responsibility was mitigated by the pragmatics of clinical duties, time constraints, their duty or care and concerns over potential trial burden. A concept of fair selection was further complicated in the context of a particular class of trials which practitioners referred to as *'wonder drug trials'*. They positioned *'disease modifying'* or mutation specific targeted novel drugs with a corrective potential as being eligible for this distinction. Following the discovery of the 'CF gene' in 1989 these targeted approaches are aimed at improving the mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which are now well established as the genetic basis of the disease (Brodlie et al., 2015; Griesnbach &

Alton, 2013). The most frequently cited of these trials were the '*Vertex*[13] *trials'*, which practitioners identified as commercial trials requiring competitive recruitment strategies.

> *The Vertex study is that there's a lot of publicity about on the forums and the internet and they think it's going to be disease modifying 'stroke' cure, they use the word cure, which I don't encourage, they're queuing up for those.* Doctor 6 (adult)

> *The recent studies on these new correctors and potentiators with CF they have they have had no trouble recruiting at all.* Doctor 9 (child)

In stark contrast to other types of trials, practitioners remarked that there were not enough of these trials for the numbers of patients who wanted to participate, in either the paediatric or adult settings. Practitioners also speculated that increasing public awareness and trial experience might be leading to patients being drawn to trials that they have judged will give them the greatest likelihood of a significant personal benefit to their health.

> *That's why recruitment for some trials is just not as fast, because if people think it's a real disease modifying... I mean we are getting to the stage now with it, oh it's another nebulised antibiotic. Whereas, oh something that affects the gene, is that a potential cure, queue up. People are getting selective; they'll buy in to the trial that they think is going to give them the best return.* Doctor 6 (adult)

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[13] Vertex is an American-based pharmaceutical company, which since 2014 has been involved in the development of novel mutation specific therapies for the treatment of CF (Timmins,2017)

Furthermore, despite practitioners' reluctance to speculate about the curative potential of these drugs, they understood the desire of patients and parents to focus on the promise of cure or the life changing potential of these novel drugs. Adult practitioners also described patients as being *'quite desperate for a cure'* due to their deteriorating health.

> *A lot of patients, of course, they are desperate for a cure, and they will latch on to things, and you can see that for most of our patients, apart from there is one group, one gene type that they are almost ready to go with something for that group of patients. The majority of them which is Delta 508 which is the most common and more severe they are nowhere near to finding anything to help with those patients. And of course, some of them are, they are quite desperate for something […]*
> Nurse 6 (adult)

A patient's hopefulness for promising treatments was complicated by the disparity between the treatments available for individuals with different CF gene mutations, with the most severe and the most common gene mutation being the furthest away from life changing treatments. Some practitioners described how patients felt marginalised or undervalued when they were not made aware of, or given the opportunity to enter these '*wonder drug trials*'. Some conveyed a sense of disappointment on behalf of their patients that these opportunities were not available.

> *They have to put up with so much, and I know how willing they all would be, they are always asking, with the different trials that are going on with the nebulised treatments, they are having some good results, and they come, and they say when can we have a go with this.* Nurse 1 (child)

> *If there is anything you know they will ask about it I think because we don't really have access to it* [the trial] *you know I am always saying well we won't get asked because we are not big enough centre and I think they feel like the second class citizens because they are not part of these big centres that always get all the renowned things really.* Nurse 5 (adult)

One practitioner described how an individual was *'really really angry'* about not being informed about an ongoing '*wonder drug'* trial at her CF centre, despite this patient not being eligible at the time of the trial. Practitioners also expressed concern about the effort and hope patients were prepared to invest in these '*wonder drug trials'*, whatever the costs.

> *Gene therapy, for instance, people were really keen to get on that trial because they think, oh its gene therapy, but a lot of them are going to be doing a lot of work for the study […].* Doctor 6 (adult)

One practitioner openly described '*struggling'* to balance a family's right to know about '*a wonder drug trial'* that they were eligible for, with her concern about the burden of the trial for this particular family.

> *As kind of a responsible researcher I was struggling with that one because[…]sometimes you just think, I don't know, have I got the right to sort of say, "This trial's going on, but you're not in it because I don't think it's feasible that you travel to London all the time," or should it be their decision.* Doctor 4 (child)

As it turned out, the trial was employing competitive recruitment practices and the trial became full before they *'might have been able to get somebody in*'. This practitioner's uncertainty about where his duty of care to act in the best interests of

the families ended and his responsibility to empower families to engage with research began, illustrated the psychological and moral intricacy of being a '*responsible researcher'* in an ever-changing research environment.

7.4 Summary

All informants across all sub-groups conveyed moral and psychological dimensions to their construction of a fair research offer. For the patient group, an acceptance of both the dependency of medical progress on clinical research and the optimism of scientific ambition characterised this discourse. The two most prominent features of this discourse were a sense of moral responsibility and the processes of hope. Informants rarely conformed to the normative assumption that patients enter trials expecting a direct clinical benefit. Rather, these individuals hoped for the best personal outcome, a hope which was bolstered by a broader sense of optimism related to the promise of progression through research. Remaining hopeful that a '*vested interest*', in their own or their child's condition would ensure potential future benefits for themselves and other people with CF, seemed a realistic prospect, given that many individuals with CF are now living into adulthood (CF Trust, 2017).

Furthermore, an informants' sense of hope was typically reinforced by a broader moral motivation, or obligation to participate for a common good and fulfil their share of this responsibility. Informants also accepted that progression is dependent on willing volunteers and from this stance, their sense of hope was enmeshed with a moral responsibility to be a willing participant. A sense of hope derived from the promise of research became all the more real when they became one of the willing participants. In many respects informants' accounts of their acceptance of research as a common good parallel the views embodied within current research practices and ethics guidelines. Consistent with guidelines, informants largely viewed

research participation as contributing to the improvement of future treatments and something morally commendable rather than morally obligatory. Nevertheless, at times informants spoke of their sense of moral responsibility in terms that were more pressing – that is, as a sense of '*duty*' or '*obligation*' to participate.

Consistent with patients and parents, practitioners' accounts of trial recruitment also included a psychological and moral dimension, albeit from the other side of the exchange. Practitioners had to balance their personal interests with the interests of their patients in order to negotiate their role as a '*responsible researcher*', amidst a changing personal career trajectory and shifting research environment. Consequently, their formulation of recruitment oscillated between unbiased marketing, asking a favour, invoking moral responsibility, or a virtuous act. This fluctuation reflected the delicate balance required within this distinct clinical encounter in which a practitioner must balance trial uncertainty, the generalised aims of research, and their duty to provide optimal care and their own personal values and interests. This discourse also highlighted the work that practitioners engaged in well before they ever embarked on recruiting a patient to particular study, to make sense of both the right way of approaching people and the fairness of a research offer.

CHAPTER 8: DISCUSSION

8.0 Introduction

The main findings of the case study are brought together in this chapter and discussed within a conceptual framework developed from them. I will consider the wider relevance of the findings in relation to the existing literature before examining the implications of the findings for policy and practice and future research. I will then discuss the study's strengths and limitations, make suggestions for future research and provide a brief conclusion.

8.1 Study Findings

An exploratory qualitative case study in a stable underrepresented population was carried out to provide a detailed, in-depth understanding of the nature and complexity of the phenomenon of trial recruitment. Aligned with a constructionist position, the aim of this case study methodology was not to discover an external reality but to construct a clearer picture of the phenomenon under investigation through integrating interpretations of situation and context (Stake, 1995). It is rare for there to be a single explanation for any aspect of the social world, and this study was no exception. Firstly, these findings characterised trial recruitment as a complex psycho-social phenomenon. I found that informants' negotiation of the recruitment process was multidimensional and variable according to attitudes, experiences, personal circumstances and trial design. Informants engaged in weighing up a multitude of factors which involved intricate trade-offs and personal value judgements, and which were socially situated according to the family context, clinical relationships, the health care system and the research and scientific enterprise.

Nevertheless, this exploratory qualitative case study was able to offer a fresh look at this complexity. Explanations in qualitative research are usually framed as conjectures rather than accounts of deterministic causes and involve making an argument or 'case' (Ritchie et al., 2014; Strauss & Corbin, 1998; Stake, 1995). My case for understanding how people make sense of clinical trial invitations was centred on informants' constructions of a 'fair research offer'. This investigation indicated that informants worked to construct satisfactory accounts of their decision to consent or decline which centred on personal perceptions of fairness.

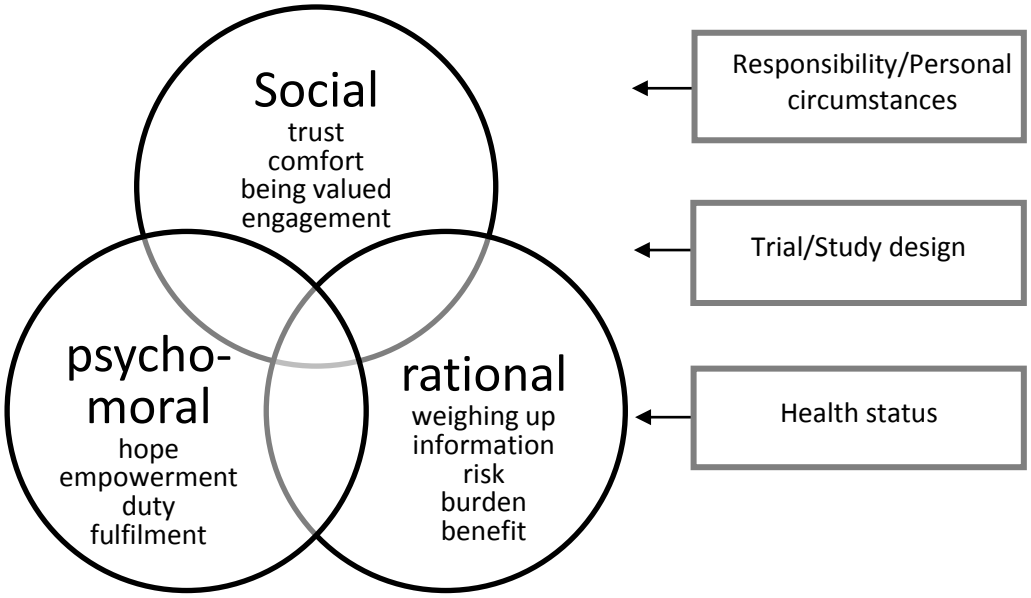
These personal judgements of fairness could be understood according to three prominent interrelated conceptual patterns or discourses I discerned from informants' accounts of recruitment – a rational, social and a psycho-moral discourse. The rational discourse illustrated how informants used their *'logical head'* to '*weigh up'* the costs and benefits, to assess the safety or worth of a particular trial or study. The social discourse illustrated how informants' accounts of recruitment were contextually and relationally dependent, within which a framework of trust was pivotal. The psycho-moral discourse illustrated how informants worked to construct a moral and psychological account of their recruitment experience, in which a sense of moral responsibility and psychology of hope were most significant.

From a constructionist position, these discourses are best viewed as interpretive devices that illustrate a set of tendencies as to how informants made sense of trial recruitment. How any individual orientated themselves to the idea of being a human subject was dependent on how they actively constructed their accounts in relation to these three prominent discourses, which were common across accounts. There was a multitude of factors which had the potential to influence how individuals drew upon these discourses. The most prominent of these included: i)

perceptions relating to a participant's health status; ii) trial design and, iii) an individual's personal circumstances including their roles or responsibilities, that is, whether they were acting as a practitioner, parent, an autonomous adult or a child within a family context (*Figure 8.1)*.

Informants made personal judgements of fairness which took different forms depending on their personal circumstances and sense of responsibility. Parents acting on behalf of infants and young children focused on acting in the child's best interest, which involved balancing both parental responsibilities and personal values. Parents of older children focused on negotiating the young person's level of involvement in decisions according to pre-existing family dynamics.

FIGURE 8.1: A conceptual framework of recruitment: judging the fairness of a research offer



Adult patients balanced their health status, past research experience and personal values to make sense of and respond to the invitation to enter a trial. Practitioners illustrated the delicate balance required for the *'unbiased marketing'* of trials, in which they considered their duty of care to patients, inherent trial uncertainty, *'a pressure of numbers'* and their own personal values.

8.1.2 A rational discourse: 'weighing things up'.

For the most part patients and parents were keen to present themselves as rational decision-makers, describing themselves as engaging in a careful, deliberate weighing up of the costs and benefits in which judgement of risks were prioritised. Informants wanted to ensure that the trial participation was not going to be detrimental to their health. They also wanted to ensure the trial was something of value and worthy of their time and effort. Practitioners were also keen to ensure that trials they had agreed to become involved in were not too onerous for their patients.

While informants understood that in principle randomisation was the fairest way to conduct meaningful research they also accepted how personally the design had the potential to feel unfair. Certain trial designs, such as a cross-over trial or preference trial where everybody had a chance of receiving the new treatment or their preferred treatment, seemed intuitively fairer compared to the '*lottery*' of the standard RCT. Consequently, how informants negotiated the risks and uncertainties inherent in clinical trials was central to their view of a research invitation they felt comfortable accepting.

Patients and families spoke of the significance and expectation of being given appropriate, accurate information and time to consider it. Practitioners

acknowledged their legal obligation to provide adequate, impartial information. Consequently, an aspect of their accounts corresponded to normative models of decision-making (Hardman, 2009; Madsen et al., 2007) which presupposes that a 'rational' autonomous patient facing a research invitation will take account of all the available information and assess the likelihood of tangible risks and benefits.

Patients and parents embraced a more far-reaching version of autonomy as relational and interdependent, as opposed to the view of autonomy as (independent) self-determination (Kukla, 2005). This view of autonomy extended beyond trust based on tangible information and incorporated both trust in their judgements and trusting deference towards practitioners. Equally, practitioners recruiting within an existing relationship were more comfortable tailoring information according to individual needs; prioritising respect for a patients' or parents' preference for the level of information, as opposed to attempting to achieve a one size fits all 'valid' consent. Furthermore an (independent) self-determination version of autonomy was not meaningful in the family setting, where findings illustrated how children worked in partnership with parents and practitioners.

Medico-legal requirements relating to the informed consent process were considered essential to authenticate a research offer as something legitimate and trustworthy, and hence integral to the construction of a fair research offer. How informants negotiated their engagement with trial information varied according to their own personal values and priorities and was subjective and contextually dependent. Making sense of trial recruitment involved a complex set of interdependencies, which extended beyond the rational consideration of trial information and procedures, and was also intertwined with social, psychological and emotional factors.

As extensive research exists detailing how many patients and families fail to achieve the level of understanding researchers have deemed necessary for 'valid' consent (Dawson, 2009; Sugarman et al., 2005; 1999; Simon et al., 2003; Corrigan et al., 2003; Ondrusek et al., 1998), this study did not focus on understanding per se. However, these findings provide insights into why many participants may fail to fully understand all aspects of a trial and their recruitment. Clearly, if an individual chooses not to engage with the trial material, they will be unable to obtain full knowledge of the information.

8.1.3 A social discourse: 'feeling comfortable and valued'

The findings illustrate the significance of considering trial recruitment as a social interaction involving a '*human approach'* with successful recruitment resulting in a mutually agreed ongoing relationship, rather than simply focusing on the point of consent and numbers accrued. Furthermore informants emphasised the importance of recruitment that involved an interactional dialogue, which facilitated open discussion, in which concerns could be adequately addressed, rather than simply imparting formulaic information.

Interpersonal qualities of the recruitment exchange had the potential to influence an individual's initial receptivity and engagement with the idea of participating in a trial. These findings also suggest that the socio-emotional character of the exchange was particularly significant where an individual's belief in research was tenuous, or past clinical experiences had been problematic or where emotion was heightened.

Practitioners viewed recruitment as being outside of their comfort zone and highlighted the significance of tenets of competent communication, such as empathy, active listening and honesty as essential scaffolding for successful

recruitment. Informants indicated there was a '*right way*' to conduct recruitment which involved someone very approachable who was engaging with the '*right person skills*', and the expectation that the recruiting practitioner should go the extra distance to ensure a successful social exchange in a less familiar context.

Integral to this successful approach was the importance of informants feeling valued, which was conveyed by a face-to-face approach wherein a practitioner was prepared to give them time and consideration according to their needs and priorities. Informants were reassured by the association of a practitioner involved in their care or recruitment occurring within a familiar context, in which research was presented as something endorsed, valued and part of the system, as opposed to something '*out of the blue*' and '*left field* '. However familiarity also had the potential to blur the distinction between research and clinical care, serving to downplay the value of the trial or participation in it.

Parents and practitioners viewed a process of trust as crucial to their construction of a fair research offer and practitioners viewed it as a principal reason why patients and parents agreed to take part in clinical trials. Informants' perceptions of trust extended from parental trust in the family context, to interpersonal and institutional trust. On the whole informants trusted the practitioners who were inviting them. In situations where a recruiting practitioner was unknown, informants spoke of the significance of trusting the hospital and the research infrastructure. Trust instilled confidence and had the potential to counter concerns about risk and uncertainty. Trust also appeared to ease the cognitive effort of the decision-making responsibility, which was particularly valuable in the context of parents of infants, who described a heightened sense of responsibility to act in their child's best interests. Lack of trust in a recruiting practitioner or distrust in the idea of a clinical

trial was evident in the context of trials that informants had declined. Practitioners worked hard to maintain their trustworthiness by engaging in their own personal balancing of harms and benefits. On occasions, practitioners deemed an offer as unfair for a particular patient at a given time, resulting in a decision not to approach them. There were also instances where practitioners viewed specific trials as having sufficient harms or insufficient benefits, for the trial not to be taken on at a particular centre or to be taken on with a reduced commitment.

In the CF setting, trial recruitment typically occurred within a familiar clinical setting, which highlighted the significance of trust and continuity in the recruitment context. Being invited to become a 'human subject' or inviting someone to become a 'human subject' required a patient, parent or practitioner to go outside their usual roles and responsibilities. To make sense of this novel situation, informants drew on the social norms of the healthcare and family context.

8.1.4 Psycho-moral discourse: 'Doing my bit and hoping for the best'

A unifying strand throughout informants' accounts was their work to construct an offer which was aligned to their values and personal interests. Where individuals had agreed to participate in a trial they emphasised the judgements they had made concerning moral responsibility and hope, but such accounts were less prominent in the accounts of informants who had declined.

Many informants compared a willingness to take part in research as akin to having '*good morals'* , whereby an individual's sense of moral responsibility was

inseparable from the warm glow'[14] derived from partaking in something perceived as morally commendable. A view which ran counter to that of altruism as an intrinsically selfless act. Informants spoke of contributions to furthering research, not as altruistic but as fulfilling a moral responsibility , one in which everybody should try and '*do their bit*' and '*give back*', to reciprocate for the previous contributions of others to research and care.

Hope was also a significant factor in the construct of a fair research offer and extended beyond a personal hope for the best personal outcome, to include a belief in a personal and generic progress narrative of modern medicine and the psychology of an optimistic, hopeful outlook. Hope also had a therapeutic value in countering the interpretation of risk and the uncertainty of trial participation, and equally in countering the uncertainty of living with an altered future.

Psychological and moral dimensions of informants' accounts were often constructed prospectively, rather than as post-hoc rationalisation. For instance, some informants spoke about how they had discussed the meaning of participating in research prior to the invitation, in which they had positioned research participation as something morally good and a source of hope. Furthermore, adult informants spoke about how they had been enculturated to the value of research participation when they were younger. Parents within this sample also talked about their role as a moral educator,

[14] In contrast to the standard notion of altruism involving behaviours which benefit another at a cost to oneself and without rewards, the notion of 'impure altruism' or 'warm glow' suggests a self interested motive or 'satisfaction of conscience' derived from 'doing the right thing' or having 'done their bit' (Andreoni, 1989; Becker,1974).

in which they had gradually trained their child about the importance of participating in research.

Informants spoke of participation in research as contributing to a common good, while remaining hopeful for the best personal outcome, as inseparable and aligned with their personal '*selfish*' interests. Both of these were positioned as important motivational resources in their decision to participate. Consequently their accounts did not indicate discrete motives of 'self-interest' or 'altruism', but rather an interrelated psycho-moral discourse in which informants were working to make an invitation to be a 'human subject' personally meaningful.

Practitioners regarded a patient's hope for the best personal outcome when participating in a trial as '*human nature'*. Indeed, it could be argued that the whole of the research enterprise is based on the hope or expectation of progression. Furthermore, while practitioners accepted the scientific principle of equipoise, they remained hopeful like patients and parents that the trial drug or intervention would prove to be effective. Practitioners indicated that it would feel unethical to enter a patient into a trial which they did not believe or hope that the trial drug had the potential to work. While hope defined by a practitioner is typically viewed as a something rational and underpinning the aim of research, hope expressed by a patient or parent has the potential to enter into the realms of misconception.

Practitioners also had to negotiate the inherent ethical tension concerning their duty of care to their patients and the requirement to engage in research to further scientific knowledge as a '*responsible researcher*'. Consequently they also drew on a psycho-moral discourse to negotiate this disparity, which varied according to their orientation to their role, and research context. This variability was reflected in the

repertoire they used to describe the recruitment process which included marketing metaphors, highlighting the exchange dimension or the cost of helping by describing research invitations as '*asking for a favour'*. This variability in how practitioners constructed recruitment reflected their work to accommodate the change in dynamics which occurs in the context of recruitment. Consistent with patients' accounts, an altruistic motive, to contribute to the common good, was not enough to construct their view of a fair research offer. They also judged the study in relation to their own personal interests and what they hoped to achieve by committing to a trial and their engagement with research was nuanced and personally negotiated. For instance, personal orientations to a particular trial in which personal equipoise was tenuous, or a practitioner had a concern regarding cost-benefit ratios, had the potential to influence a practitioner's commitment to and faith in a trial.

Informants' accounts of research participation conveyed a sense of personal grappling, reflecting the delicate balance required to negotiate personal interests in the context of uncertainty, responsibilities and hope. A degree of therapeutic optimism seemed necessary for both a practitioner to accept '*the morality of a study'* and for a patient to accept the potential burden of trial participation, because without a belief that the trial could lead to something better in the future, what would be the point of trying.

I viewed this psycho-moral discourse as reflecting the cognitive work in which potential participants and recruiters must engage, to feel at ease and free from dissonance amidst the inherent tension in clinical trials and the role of being a 'human subject'.

8.2 Main findings in relation to the existing literature

8.2.1 What makes research feel fair: a personal balance account

The findings of this study correspond with the existing evidence which characterise trial recruitment as a challenging, intricate phenomenon which is contextually defined (Tromp et al., 2016; Ulrich et al., 2012; Truong et al., 2011; Fayter et al., 2007). How an individual decides whether to take part in clinical research has typically been defined as involving the weighing up of a multitude of factors, a process that has been described in the literature as a 'clustered reasoning' (Ulrich et al, 2012; Townsend & Cox, 2013; Madsen et al, 2007; Verheggen et al, 1998; Snowdon et al, 1997).

Academics and practitioners have been grappling with the morality of performing experiments on human subjects for more than a century (Brown et al., 2004). Similarly, informants in this study, like those in other studies, also grappled with the dilemmas involved in making sense of the role of 'human subject', 'volunteer' or 'research participant'. I viewed informants as grappling with these dilemmas in much the same way as a regulator or bioethicist grapples with the standards required to deem a research protocol as ethical. Moreover, informants' accounts of how they judged the fairness or acceptability of a research offer often reflected elements of the wider ethical framework used to determine what makes research involving human subjects ethical.

Medical ethics like other ethical discourses is concerned with the rightness and wrongness of action and although informed by moral debate, it typically operates within an established framework of values (Mason & McCall Smith, 2006). A system of medical ethics known as 'principlism', advocated by Beauchamp and Childress

(2001) has become pervasive within the bioethical literature, based on the four principles or 'pillars': autonomy, beneficence, non-maleficence and justice. While not always explicitly stated within ethical guidelines for clinical research, this framework is used to determine the standards necessary for the ethical development and implementation of research protocols (Mason & McCall Smith, 2006; Emanuel, 2000). Despite this wider framework informing the ethical conduct of research, the principle of autonomy translated into the doctrine of informed consent has become central in debates about what makes clinical research ethical and is the overarching principle upon which the process of recruitment is understood (Kukla, 2005; Emanuel, 2000). Nevertheless, findings from this study support the view that what makes research fair or acceptable for a patient, parent and practitioner include and extend beyond the confines of autonomy, to include a more far-reaching ethical framework. In some respects, informants' personal judgments of fairness mirrored facets of the broader framework of values underpinning medical ethics, including the four 'pillars'.

In the first instance, informants wanted to know the risk of harm and an acceptable cost-benefit ratio was essential to their construction of a fair offer. Informants also emphasised the significance of action which foregrounded their individual welfare, such as displays of empathy, competence, trustworthiness, and the establishment and maintenance of meaningful relationships. Informants perceived research as something valuable personally, scientifically and for the wider CF community. Assurance that the research was something of value and that they, the participant would be valued, were important to informants in countering the inherent uncertainties in clinical trials. Informants viewed receiving accurate information as integral to a fair offer and indicated the importance of having the self-determination to make decisions, consistent with their values, beliefs and preferences. Some

informants also spoke about the fair selection of participants and how the benefits and burdens of research should be distributed equitably.

This study adds to the literature which emphasises the work people must do to establish a personally meaningful,view of the role of a 'human subject' (Cox & McDonald; 2013; McCann et al., 2013; Madsen et al., 2007; Morris & Balmer, 2006). Consistent with findings in the empirical literature this study showed how informants engaged in a 'balancing of options' that extended beyond a rational consideration of trial information and procedures to include personal value judgments (Ulrich et al., 2012; Madsen et al., 2007; Verheggen et al., 1998). How patients, parents and practitioners thought about research participation often paralleled how researchers and bioethics determine what makes research ethical or 'fair'. However, informants were judging what makes an individual research offer personally 'fair' for themselves, rather than applying broad objective standards of ethical acceptability in the case of research regulators. Nonetheless, the values inherent in both situations coincided, indicating that these broader principles resonate with personal morals and that it is not only researchers and bioethicists who think about research 'ethically'.

8.2.2 Balancing risk, hope, and a sense of responsibility

Rationalising risk was central to how informants initially made sense of research invitations. The centrality of 'risk behaviour' and 'uncertainty reduction' has been reported elsewhere in the literature, particularly in the context of individuals living with uncertain futures and conditions such as CF and HIV (Lowton, 2005; Mueller, 2004). In the literature, self-interest and altruistic motives have also typically been identified as important constructs for understanding why people volunteer to take part in clinical trials and agree to negotiate risk and uncertainty (e.g. Truong et al.,

2011; Costenbader et al., 2007; Gammelgaard et al., 2006; Edwards et al., 1998; Cassileth et al., 1982). These motives have often been presented as competing or distinct.

It could be argued that a patient who undergoes extra blood tests while taking an experimental drug with uncertain clinical harms and benefits performs a purely altruistic act. However, for informants in this study, costs and benefits extended beyond the narrow lists of tangible risks and benefits detailed in study documentation, to include the therapeutic value of hope and the fulfillment of taking part in something worthwhile. Also, many informants spoke of other indirect, immediate personal benefits such as meeting new people, being part of something revolutionary and extra monitoring.

While for some informants, particularly adults, their sense of hope had been disrupted by the unrealised promise of gene therapy, parents' and adults' psychological and moral accounts of their decision to participate in clinical research were mostly indistinguishable. If altruism is not something that another person can volunteer on someone's behalf (Spriggs, 2006), it would have been reasonable to anticipate a difference across adult patient and parents' accounts. Furthermore, parents spoke of their role as a moral educator, in which they had gradually enculturated their child to the moral responsibility of participating in research, a view contrasting with the position that altruism is an intrinsic hard-wired motivational state (Batson, 2014; Preston, 2013). In addition, the role of the volunteer was viewed as something personally rewarding providing an *'inner glow'*, a finding which contrasts with the standard view of 'altruistic' acts as behaviours which benefit another at a cost to oneself and without rewards (Preston, 2013).

In the field of biology, researchers have drawn on the concept of reciprocal altruism to accommodate the disparity between the promotion of self-interest and the interests of others. (Silk, 2013; Trivers, 1971). This idea of reciprocity or reciprocal altruism is also thought to provide a more meaningful construct to understand patients' motivations to take part in clinical trials than altruism (Locock & Smith, 2011; Dixon-Woods & Tarrant 2009). Proponents of this concept assert that individuals are willing to incur costs if there is a chance the altruistic act will be reciprocated in the future. Such a sense of reciprocity was evident in this study's findings, in which informants spoke of being part of a 'cycle' in which they expressed gratitude to past generations of research participants who had contributed to improvements in treatment and a sense of responsibility to continue this cycle. Comparable findings have also been reported in qualitative recruitment literature regarding reciprocal aspects of altruism (McCann et al. 2010; Jansen 2009; Simon et al., 2006). Unlike altruism, reciprocity implies a degree of personal benefit, albeit an imagined future benefit. Nonetheless, reciprocity is still dependent on an altruistic act, and immediate personal interests are not typically considered.

Moreover, empirical evidence in the context of blood donation, considered to be an archetypal altruistic act (Titmus, 1971), has shown that a number of related processes are involved as opposed to a single construct (Evan & Ferguson, 2014). Also within the recruitment literature, there is inconsistency and variability in how altruism is constructed (Truong et al., 2011; Simon et al., 2006; Garcea, 2005). Therefore, it is plausible that those findings and the findings from this study indicate that viewing altruism as a singular construct is not adequate to account for the positive personal and social benefits derived from contributing to a common good (Batson, 2014; Preston, 2013; Scott & Seglow, 2008). Furthermore labelling an individual's motive as 'altruistic' has the potential to obscure the holistic, nuanced

ways that the informants in this study made sense of a research invitation and their own related interests, concerns and potential vulnerability.

Informants' accounts of their motive to contribute to the common good, and fulfil a moral responsibility were interwoven with various interrelated intrinsic pay-offs Consequently these findings provided further insights into related concepts, particularly 'weak' and 'conditional altruism' that have been developed to explain the relationship between self-interest and altruism, (Canvin & Jacoby, 2006; McCann et al. 2010). Rather than viewing self-interest or altruism as dichotomous constructs, the findings of my study indicate that they are part of the same psycho-moral process. Furthermore, these findings align with a growing body of work that foregrounds patients' perspectives on responsibility in health research. Within this work, personal motivations are positioned as part of the wider system of shared values, moral responsibility and social exchange (Cox & McDonald, 2013; Locock & Smith, 2011; Dixon-Woods & Tarrant, 2009) as opposed to what has become 'reified' as altruism in the recruitment literature (A Jacoby, personal communication).

The comparative focus of this study was instrumental in questioning the value of singular constructs such as altruism for understanding trial participation. Informants in this study made sense of trial recruitment according to conceptual patterns or discourses in which centred on an interrelated rational, social and psycho-moral discourse.

8.2.3 Recruitment as a social exchange

Findings from this study concurred with empirical evidence which has illustrated the significance of viewing patients' and parents' engagement with research as the beginning of a new social relationship with all its structures and requirements (Cox

& McDonald, 2013; McGregor et al., 2010). Accordingly, tenets of proficient clinical communications including feeling socially comfortable and valued, necessary for the establishment of a social relationship, were prioritised by patients, parents and practitioners over those required for imparting the 'hard facts' (Salmon & Young, 2009; Bensing et al., 2003). Consistent with existing evidence, patients and parents prioritised feeling 'socially comfortable and appropriately valued' and the importance of a sense of being cared for, in their decisions about whether to participate in clinical research. (McCann et al., 2013; Morris & Balmer, 2006; Wilcox et al., 1996). The significance of such 'socio-emotional' aspects of interpersonal exchanges has been reported across various health contexts including pre-term labour, oncology and stroke trials (Mangset et al., 2008; Madsen et al., 2007; Kenyon et al., 2006).

Patients and parents stressed the significance of meaningful engagement both with practitioners involved in the research and the very enterprise of research. This social exchange view highlights the significance of the establishment of direct social relationships upon which the success of recruitment rests (McGregor et al., 2010). Emotions are important in sustaining exchange relationships, with positive feelings such as enthusiasm or satisfaction being essential in their maintenance (Lawler, 2001; Lawler& Thye, 1999). This view appeared particularly important for younger informants who emphasised the significance of research being '*fun', 'exciting'* and different to routine clinical care.

Consistent with social exchange theories, the present study findings indicate the centrality of trust in the establishment and maintenance of research relationships (Lawler, 2001). Trust is regarded as lying at the heart of research on human subjects (De Angelis et al., 2005) but how this concept should be understood or how it

operates in practice is much less clear (McDonald et al., 2008). Findings from this study provided insights into mutual understanding and trust within the family unit, the significance of interpersonal trust between families and the clinical team, as well as informants overarching trust in the hospital and research infrastructure. They support a view of trust as a temporal, multi-dimensional phenomenon (Khodyakov, 2007) in which trust is a process formed according to strong and weak interpersonal ties; and which has the potential to influence the development and maintenance of relationships. This framework also acknowledges that trust may be based on societal institutions such as, public services or government policies. Within the context of CF clinical relationships, due to their longevity and intensity, mirrored family relationships typically based on thick interpersonal trust. This depth of trust contributed to patients' and parents' social ease and potential acquiescence to research invitations. Nonetheless, thick interpersonal trust also enabled practitioners to support families to make the 'right' decision.

Informants expressed an overarching trust and faith in the research endeavour and the scientific integrity of research. Aligned with this position is the view of research participation as a 'normative ideal' valued as a 'social responsibility' or 'moral duty' due to the expected future beneficial outcomes for the community (Fry, 2008). This view resonates with Dixon-Woods & Tarrant's (2009) concept of research participation as a 'collaboratively orientated action'. Despite most informants positioning trial participation as contributing to the public good, their decision to engage in a particular trial was still personally negotiated and contingent on judgements of personal costs and benefits and the establishment of a social relationship. However, for individuals who were the most receptive to research, it became part of their continued collaboration with their health care providers and a

valuable component of their personal trajectory for living with CF or parenting a child with CF.

8.3 Potential Vulnerabilities

Central to the development of the conceptual framework were insights gained from comparing how parents, children, adults and practitioners experienced trial recruitment. This drew attention to potential vulnerabilities that arise within the research context. These vulnerabilities were apparent in relation to:

- informants' personal expectations of a trial and potential misconceptions
- high hopes and disappointment in 'wonder drug' trials and future research
- trust and acquiescence to research invitations during recruitment in a familiar setting
- additional complexities in the child setting

8.3.1 Personal expectations of a trial: a trial as the best option

Potential vulnerabilities arose with regards to informants' blurring of the distinctions between the research and clinical role of recruiting practitioners. This vulnerability was conveyed by informants' belief that a trial had been offered because the recruiting practitioner thought it was their best option or in their best interests. This finding is consistent with the therapeutic misconception literature in which a patient's expectation that a doctor will always act in their best interests is viewed as contributing to a therapeutic bias within the research context (Lidz et al., 2002). Within the CF setting where recruitment typically took place in the context of an existing long-term clinical relationship, this expectation was heightened due to patients' and families' faith that their practitioner would always act in their best interests.

However, informants' reading of the situation appeared too nuanced to be seen as a straightforward misunderstanding, as their expectation of a duty of care was typically interwoven with indirect benefits, linked to a belief in the value of the trial and hope for future personal benefits. Furthermore, decisions about whether a patient's expectation of optimal care in the research context should be considered a misconception also hinges on faith in the principle of equipoise. Advocates of the principle of equipoise believe that RCTs are consistent with a practitioner's duty of care, as no patient is knowingly given an inferior treatment (Freedman, 1987).

Furthermore, one view of the therapeutic misconception is that whatever the benefits of a trial, clinical research involves giving up some benefits that are ordinarily part of routine care (Lidz et al., 1982). While this may be true concerning tangible trial related procedures, more important to many patients and families, were the indirect benefits of trial participation. Informants in this study were clear that the trial might not bring them direct clinical benefits and that the goal was to improve treatments in the future, even though many also hoped for the best personal outcome. However, they were aware of the increased monitoring within a trial, the feel good factor of contributing to something worthwhile and that they could return to standard therapies if their own or their child's health deteriorated. Child informants also identified indirect benefits relating to trial participation, such as the opportunity to have their routine clinical visits combined with the trial, which they perceived as being more fun and more relaxed than regular clinic visits. If patients and families perceived indirect benefits of trial participation as outweighing the costs of trial participation, to view this as a misconception seems hard to justify.

8.3.2 Hope and disappointment in 'wonder drug' trials

Potential vulnerabilities arose with regards to informants' high hopes in the promise of advancing biotechnologies and 'targeted therapies' involving mutation specific treatments (Brodlie et al., 2015). This vulnerability was conveyed by informants in their acknowledgement of their desire to '*pin their hopes'* on the potential of future research and their concern regarding the negative impact of '*false hopes'*. For many informants, particularly parents, their hope in the capabilities of research and the potential of the curative potential of future therapies provided the '*driving force'* for their engagement with all research. Informants also described how they were prepared to negotiate higher risks for trials with high hopes. Indeed, some practitioners expressed concern about families' and patients' optimism and willingness to put themselves out for the sought after '*wonder drug trials'*. These findings regarding informants' hope in the capabilities of future research is consistent with what has been labelled in the literature as the 'collective therapeutic misconception' (Woods et al., 2014; Dresser, 2002). This concept refers to an over optimistic view of the promise of research, which has the capability of biasing an individual's perceptions about clinical research.

The distinct context of CF, in which the possibility of 'finding a cure' was made more real with the landmark discovery of the first gene for a human disease (Pearson, 2009; Porteous & Dorin, 1990), presented additional intricacies to an individual's optimism. Adult informants had witnessed first-hand the unrealised promise of gene therapy, which for some had led to disappointment, and a more cautious attitude. Similarly, practitioners described their sadness at the unfulfilled expectations of gene therapy to provide a cure, particularly in CF where hope can become desperation given the ever present knowledge that the condition is life limiting. Nonetheless, many adult patients continued to accept the necessity for

research and held on to an optimistic outlook. Although adults informants were not as motivated towards research as the parents in this sample, who emphasised an optimist view of the promise of clinical research and cited their hope for a cure as a key motivator for their engagement with research.

However, parents were often conscious that their views were overly optimistic - this was a view they had actively chosen to adopt as a way of coping. Despite the burden of the decision-making responsibility and the high emotional demands of caring for a child with CF, research participation provided parents with a sense of agency in an emotive context, in which at times, they felt powerless. Trial participation in many ways became an important component of parents' personal experiences of parenting a child with CF, and they viewed being approached about a clinical trial as a significant event, particularly the first invitation. Parents also gained an intrinsic 'feel good factor' that they were doing something good both for their child's future health and for society. At times, parents themselves appeared to be acting as advocates for research, and there was a sense in which the more value they placed on something, the more value it had. This value was important in creating a sense of hope or therapeutic optimism for the future of their children.

For some parents, an overly optimistic outlook for future research provided them with their '*only hope'* for their child to have a normal life expectancy. These findings lead me to question the validity of simply compartmentalising overly high, idealistic hope as a misconception, or cognitive bias, because by doing so we may be failing to recognise a psychological need for hope in parents and patients as a way of managing life with an uncertain future. A similar concern has been raised in the empirical literature in the context of adult patients enrolling for oncology trials (Ulrich et al., 2012). Furthermore, if parents have insight into this overly optimistic view, then their high hopes for the future may be best seen as a discursive resource

for coping rather than a misunderstanding (Weinfurt, 2004). The alternative of a realistic outlook but an inability to cope may be rational but ethically questionable for a parent or patient who has to live with daily uncertainty about the future.

Nonetheless, in the paediatric context, parents' enthusiasm was potentially problematic due to concerns that they are a 'vulnerable' group who are particularly susceptible to coercion and undue influence. For trials they viewed as offering great promise, parents were prepared to convince their child, a process which they described as a form of moral training. Practitioners also acknowledged that for the most part, parents were more *'keen'* to participate in clinical research compared to children who often required '*a bit of convincing'*. However, all but the youngest children in this sample accepted clinical research as something essentially helpful and indicated they were at ease with the nature of their involvement.

Whether this parental moral training of children in relation to trials should be considered as coercion is a sensitive matter, raising questions around respect for personal family value systems and the boundaries of parental and research responsibilities (Woods et al. 2014; Bluebond-Langer, 2005; Leiken, 1993). Parents' commitment to medical research was strongly motivated by a desire to support research that represented possible benefits for their child - a realistic prospect given the long-term nature of the condition and current advancements. However, this analysis showed how susceptibility might arise around balancing the value and burden of the things a child is convinced to do.

An additional vulnerability was linked to the promise of new therapies in a context of limited access to the on-going spate of 'wonder drug trials'. For the most part, parents and patients were keen to access these trials but they and some practitioners

were concerned about the equity of access to these trials. Indeed, some described these 'cutting edge' trials as having great promise and prestige, but as the trials tended to be limited to leading research hospitals, these descriptions were often accompanied with a sense of missed opportunity or inequity of access. In competitive pharmaceutical trials with the number of eligible potentially willing participants often exceeding the number of places avialable, a converse problem to the conventional '*pressure of numbers'* and focus on recruitment rates arises. This concerns fair selection and equity of access to the potential benefits of research. This problem brought into view the role of the *'responsible researcher',* where the practitioner must balance the principles of fair selection and a duty of care. If knowledge about trials is considered to be a 'right', the question of universal ethically acceptable selection procedures may come under further scrutiny, particularly in the context of promising *'wonder drug trials'.*

8.3.3 Trust and acquiesence

With regards to the relational aspects of recruitment and the social context of the research invitation potential vulnerabilities arose. Within the reassuring, familiar CF setting at times parents and adults illustrated trusting deference and acquiescence of research invitations. Similarly, deference and acquiescence was evident in the accounts of child informants but expressed in relation to their reliance and dependency on their parent's guidance and support in the research context. These findings regarding deference and acquiescence could be understood as supporting the view that trust is fundamental to clinical research and to informants' decisions to participate in clinical research (McDonald et al., 2008). Individuals volunteer for research because they trust that their participation will lead to knowledge that will help to improve treatment for future patients and they trust that practitioners will minimise risk (De Angelis et al., 2004). In this study, both

interpersonal and institutional trust was pivotal to informants' satisfaction with the approach and their interpretation of a fair research offer. However these findings could also be viewed as being consistent with the therapeutic misconception literature, particularly as it pertains to patients underestimating the risk associated with trial participation (Lidz et al., 2004). In CF, where recruitment typically took place in the context of a trusting clinical relationship, an informant's trusting deference could be interpreted as tantamount to a misconception.

Informants who had been approached on numerous occasions implied that they had become habituated to research invitations. A similar finding has been reported by Lowton (2005) in which CF patients conveyed an 'ease' in being involved in research. Resembling Lowton's (2005) findings, some informants in this study indicated that past positive research experiences, combined with an approach by someone trusted, reduced the cognitive and emotional work they engaged in when approached about a new study, potentially leading to less vigilance about potential risks. However, this habituation usually occurred in relation to simpler studies or low-risk trials. For the most part patients, and parents' prioritization and personal judgements of risk - and trusting deference to health professionals and the hospital infrastructure - usually coexisted.

A further vulnerability concerning trust arose from the intensity and longevity of the clinical relationship in CF, in which patients and families may experience a particularly strong sense of obligation to the clinical team. Moreover, within a context such as CF, a sense of obligation was also heightened for some informants, due to a concern that others may not take their fair share of the research responsibility. While most patients and families spoke about feeling comfortable saying no to research invitations from known practitioners, some informants were

inclined to feel a sense of obligation to the clinical team. However, this obligation was personally orientated and was typically combined with a wider moral responsibility to contribute to the common good and take part in something worthwhile. In addition, being approached by a trusted practitioner instilled their faith in the potential value of the research and the socio-emotional reassurance they derived from being approached by someone known, fostered their receptivity to the trial. Ultimately, the extent to which an individual's decision-making involves trusting deference to health professionals and whether this is viewed as a 'misconception' reflects the ongoing debates about the limits of informed consent and definitions of autonomy (Corrigan et al., 2009; Manson & O'Neill, 2007; Kukla, 2005).

8.3.4 The 'complexity' of the child setting

Within this study, the special 'complexity' that is often attributed to trial recruitment in the paediatric setting (Gibson et al., 2011; Caldwell et al., 2004; Punch, 2002; Olechnowicz et al., 2002) was most notable in the accounts of parents. The responsibilities associated with the role of parenthood, which is characteristically viewed as an 'extraordinarily demanding undertaking' (Blustein, 2012), were heightened in the context of CF. Furthermore, parents constructed their responsibility in line with normative assumptions around acting in the best interests of their child. This exacting high ideal, of parental authority, which it has been argued is too demanding (Salter, 2012; Blustein, 2012) served to emphasise the weight of responsibility parents felt in this uncertain context.

Parents' concerns for whether their actions in relation to research were the best for their child were particularly intense when their child was too young to be involved in the decision about research or the parents had limited research experience. Also

the emotional context appeared to reduce parents' confidence in their ability to 'do the right thing'. By placing their trust in the CF team and the hospital that has been caring for them, parents reduced the emotional burden of this onerous responsibility. However, further complications arose when a child was considered ready to be involved in research discussions. From this point, parents' responsibilities extended to include negotiating both their child's best health interests and the psycho-social best interests of the child and the wider family. How parents negotiated these interests and their child's involvement was influenced by the age and developmental stage of their child and their interpretation of their role as parents, which determined the family dynamics or '*family set-up '.*

These findings parallel previous evidence on the acute sense of responsibility felt by parents to do the right thing in an uncertain trial context (Stewart et al., 2012; Woodgate & Yanofsky, 2010; Shilling & Young, 2009; Snethen et al., 2006; Pletsch & Stevens, 2001). However, the comparative focus made parents' vulnerability all the more apparent when compared to the noticeably less 'complex' view of responsibility in the accounts of child and adult patients.

Aligned to parents' responsibility was a child's dependency on the authority of their parents, which included different degrees of negotiation and sharing, through to autonomous decision-making, comparable to that found in the accounts of adult patients. The balance of a child's responsibility and dependency in the research context was primarily determined by their family's model for managing roles and responsibilities, and this balance mirrored the child's involvement in wider clinical decisions. That is, these children had become accustomed to patterns of communication in the clinical setting, and as recruitment typically occurred in this context, research was not viewed as something particularly 'complex' or untoward.

This finding is consistent with previous evidence on the importance of considering existing family dynamics in the recruitment context (Oulton et al., 2016; Madden et al., 2016; Snethen et al., 2006; Broome & Richards, 2003), which have led to recommendations to move towards a family approach to consent, and to relaxing the distinction between assent and consent (Foreman, 1999; Gibson et al., 2011). However, children are socialised to respect the role and authority of parents and other adults (Rossi et al., 2003; Leiken 1993; Susman et al., 1992) and there is concern that a more family orientated consent may potentially weaken the child's voice and increase a parent's influence in discussions (Balen et al., 2006; Alderson, 1999). While a sensitive respect of family dynamics appeared integral to meaningful recruitment in the child setting, where these factors are in tension, the significance of assent comes into play as a strategy or safeguard to prevent family coercion or undue influence (Simon et al., 2004). This study supports the view that for children to participate in the decision-making process in a meaningful way, the existing family dynamics need to be respected, at the same time as ensuring that decisions are free from coercion and the child is aware of the procedures they are expected to undergo (Madden et al., 2016; Bluebond-Langer et al., 2005).

This study also supported other findings indicating that children's experiences were more influential on their level of involvement and awareness than their age and developmental stage (Broome et al., 2001). Children appeared capable of understanding what they were supported and permitted to know, or what the situation dictated that they needed to figure out at a particular time. Parents were instrumental in shaping broad patterns of involvement, particularly for children who were not yet teenagers. Parents and practitioners recognised that sometimes parents preferred to protect their children from certain information, particularly in the *'in-between'* years and particularly from information about their illness trajectory.

These families illustrated a bounded type of sharing in which parents engaged in a lot of work to establish the terms of the negotiation, involving a delicate balance of nurturing and protective roles.

The accounts of some of the older children illustrated additional intricacies regarding the evolving family relationships, in which roles and responsibilities were transitioning. Teenagers described how they still felt reliant on their parents, yet parents and practitioners often felt duty bound to encourage autonomy. Furthermore, a potentially overlooked tier of 'complexity' in the paediatric setting was a child's sense of responsibility towards their parents. Children negotiated their roles according to changing circumstances and expectations, which at times required them to engage in a tactful and restrained presentation of their developing autonomy to diplomatically manage their parents' feelings. Comparable findings have been reported elsewhere in the literature involving children with life-shortening illness, and research invitations where children have been shown to respect and act to preserve the social order of their families (Bluebond-Langer et al., 2005). However, this study also highlighted the extent that adult patients similarly deferred to social influences when making decisions concerning participation in trials (Dixon-Woods & Tarrant; Leiken, 1993) many still relying on parental support. Moreover, a trusting deference to practitioners and the institutional field were integral to parents' and adult patients' construction of a fair offer. The difference in the child sample was that their deference was mainly to parents rather than to a practitioner or institution.

An important distinction between adult patients' and the accounts of parents and children was adult informants' emphasis on current '*stage of health'* and the construct of time. Their judgements of risk and burden were heightened in a context

of their deteriorating health, time constraints and more intensive treatment compared to the child sample. Therefore adult patients emphasised the need for research of high value or with a significant return, to be able to offset these burdens, or looked for research in which their efforts were valued accordingly. In some respects, due to the deteriorating course of the illness, adult CF patients appeared more vulnerable than children. While both children and individuals with an incurable health condition comprise 'vulnerable' groups according to research regulation (Declaration of Helsinki, 2013; Corrigan et al., 2009; ICH GCP, 1996) these findings support the view for a more reasoned, nuanced understanding of vulnerability (Nuffield Council on Bioethics, 2015; CIOMS, 2016; Sieber, 2008).

Additional complexity in the child setting, at least in relation to practitioners' accounts of their role, was largely unsupported by the present study. Paediatric practitioners viewed navigating the dynamics of families as part of their daily work and did not foreground it as something more complex compared to adult practitioners. Nevertheless, comparable to the parents' accounts of their interpretation of their role in the research context both the paediatric and adult practitioners' accounts conveyed an overarching complexity in relation to their balancing of multiple roles. This complexity was evident in how practitioners constructed their responsibility in research, where they had to promote the best interests of their patients and achieve the role of a '*responsible researcher*'. To navigate this complexity, practitioners spoke about the significance of assessing the worth and morality of the study, judgements which were based on the fusions of professional and personal values to determine the fairness of a research offer. An additional tier of complexity for practitioners, whose role was not predominantly research-based, was linked to the professional return for their engagement within research. These findings support and extend evidence that indicates that the role of

recruiting patients can be challenging both intellectually and emotionally (Lawton et al., 2015; Donovan 2014; Tomlin et al., 2014; Ziebland et al., 2007).

In summary this study has extended recruitment research beyond looking at either adult or child factors (Simon et al., 2004) and in doing so it has illustrated how meaning is negotiated according to the 'social realities of family life' (Bluebond-Langer et al., 2005). The findings show that the ways in which adult patients made sense of recruitment shared many common features with children's accounts. Adult patients and some children, particularly teenagers, alike judged a research offer in terms of its fairness, and this judgement typically hinged on whether they considered the trial or study to be worth their time or effort. These judgements seemed less onerous than those of parents, who typically had more stringent aspirations in trying to make the '*right'* or the *'best'* decision on behalf of their child. This is not to say that these adults and teenagers took their decision-making lightly, but that they made sense of these decisions relative to their particular situation. Adult patients had more clinical and research experiences and appeared more accustomed to making difficult decisions compared to both parents and children; while children's decision-making was founded heavily on trust. In contrast, parents had to balance their own child's immediate and future 'best interest', with their values. Consequently, their decisions appeared weightier compared to those of adult and child patients.

8.4 Implications of this study

This section explores the potential implications of the findings of this study for policy and practice of trial recruitment.

8.4.1 Recruitment Policy

According to the regulatory and ethical literature, the ideal recruit to a clinical trial is voluntary, competent, adequately informed and eligible. In contrast to this idealised view of research 'participants', this study emphasised the additional significance of feeling comfortable, valued, secure, engaged, empowered and supported to be part of something that makes sense and is of value to themselves and others. How patients, families and practitioners negotiated the fairness of a research offer was according to their personal interests, which extended beyond the medico-legal requirements of informed consent, to include the social context and a broader psychological and moral dialogue. Consequently, these findings suggest there may be a need to broaden policy on 'recruitment' to ensure that 'patient's perspectives' inform the guiding principles of trial recruitment. Predominant discourses on recruitment focus on the number of participants accrued, informed consent, and recruitment strategies, which do not adequately capture how recruitment is constructed by those involved. For these informants, meaningful engagement was at the centre of their construction of a fair research offer.

If recruitment is viewed as meaningful engagement, the definition of 'successful' recruitment changes. From a discourse on accrual, successful recruitment is typically seen as a patient's enrolment in a trial, with recruitment strategies primarily aimed at increasing recruitment rates. In contrast, the discourse on informed consent is first and foremost concerned with strengthening the ethical conduct of research, with successful recruitment equating to a patient's full understanding of the twenty points of informed consent. For these patients and families, feeling valued and a belief that they would potentially be taking part in something of value and worth, appeared to be at the heart of meaningful engagement.

Meaningful engagement captured both the direct personal engagement with the recruiter to make sense of the research offer and a more far-reaching engagement with the wider enterprise of research. Positive engagements were valued, even where patients were not in a personal position to participate; they remained more receptive and open to future research offers following successful engagements. In relation to an individual's wider engagement with research and their belief in a progress narrative of modern medicine, the fairness of the promises, expectations or access to the benefits of medical research were all aspects of meaningful engagement.

These findings indicated that recruitment policy will benefit from the continued development and implementation of practices which foster engagement with research, in which the meaning of research is made more visible and tangible. The advance of online resources (e.g. I am Research campaign, NIHR, 2017; Heathtalk.org, DIPEX, 2001), which share the views of others who have participated in research, appear to represent a significant development in this area which is reinforced by the findings of this study. However, patients and families expressed a reticence about pursuing information about clinical trials independently, without the assurance of their practitioner. This potentially brings into question campaigns directed at encouraging individuals to be proactive in their engagement with research (e.g. the "Ok to ask" about clinical research campaign, NIHR, 2014). Patients' families and practitioners in this study spoke of how the interpersonal quality of the approach instilled both value in them as potential participants, and the value and integrity of the trial itself.

Further developments may include accounts of trial participation described by 'participants' themselves, published in patient information leaflets or via media

resources and trial information web links. Currently, due to concerns about coercion and impartiality, ethical committees will only permit tangible costs and benefits together with an acknowledgement of the generalised aims of research to be included in a patient information leaflet. However, the indirect benefits of trial participation are typically how an individual makes sense of the experience and constructs their view of a fair offer. Furthermore, for a child who may have difficulty relating to an abstract concept of a clinical trial or the idea of future benefits, knowing what the experience of participating in a clinical trial feels and looks like from the perspective of another child has the potential to provide information in a way that is more meaningful to them.

Concerns regarding trial recruitment have been a long-time issue, with recruitment of large enough numbers becoming increasingly difficult and these findings could help with this issue. In summary, this study lent support to existing empirical evidence, emphasising the need to support positive experiences and sustained, meaningful engagement with research (Gillies & Entwistle, 2012). However, to reconceptualise recruitment within a broader framework of meaningful engagement would require potential policy changes and a change in how the discourse and knowledge on recruitment are constructed.

8.4.2 Recruitment Practice

These findings indicated that a high level of proficiency in clinical communication was required for optimal recruitment, which may not be achievable through standard clinical communication training. A practitioner, during a recruitment encounter, must navigate the socio-emotional needs of a patient and the various biases that may arise from the framing and imparting of medico-legal information. This encounter was potentially made all the more challenging in a context where the

patient was unknown, and the practitioner was unaware of personal or medical issues which had the potential to influence the interaction. These findings indicated that where possible, there should be close collaboration between individuals involved in the recruitment process and clinicians involved in a patient's care, to ensure awareness of social, clinical needs or any issues which may require '*special management*' e.g. a needle phobia and employment issues.

Consistent with trial communication research, this study highlighted the significance of acknowledging recruitment as a sequence of moves in which first and foremost a recruiter must establish a shared understanding of the patient's illness or health status relevant to the trial (Brown et al., 2004). In addition to an empathetic understanding of an individual's current health status, patients and families spoke about the importance of feeling comfortable and valued. Moreover, a face-to-face approach was considered essential by patients and parents in an emotional context or if the practitioner was unfamiliar to the patient. These findings also suggest that discussing an individual's usual approach to decision-making has the potential to facilitate personalised understanding and satisfaction with the engagement and the decision-making process. Involvement in the decision process at the patients' and parents' preferred level was identified as particularly important for 'meaningful' recruitment in the family context.

This study suggests that the way people are initially approached, 'first impressions' and the selected informational content and emotional tone of that initial engagement have the potential to influence the establishment and maintenance of the research relationship, integral to successful recruitment. Therefore, recruitment practices need to be developed which prioritise the facilitation of an active dialogue

that privileges open discussion rather than practitioners approaching the situation as one where the onus is simply on giving or imparting information.

Informants viewed trust as essential to successful recruitment and this was crucial in how comfortable patients felt with the initial approach. The context of CF in which ongoing care is centred on trusting relationships provided insights into the prerequisites for trust or the motifs of trustworthiness which included:

- Empathetic engagement
- Display of knowledge, competency and sensitivity
- Evidence of regulation
- Evidence of qualification, clinical and research experience.
- Evidence of connection with the hospital.
- Track record in research

I hope that a published summary of my study findings will be informative and beneficial to researchers engaged in the task of 'recruiting' participants to trials or those who are about to embark on the task. These findings will also have particular relevance to practitioners working in the field of CF and other chronic conditions.

8.5 Strengths and limitations

As described in Chapter 1, the aim of this study was to use a case study of an underrepresented clinical population, to generate theoretical and empirical insights into the phenomenon of trial recruitment. Consequently, it is important to consider the strengths and limitations of using CF as a case study to examine trial recruitment and the extent to which the findings are transferrable to other contexts.

The case of CF provided an opportunity to compare recruitment experiences across adult and child settings within an easily defined patient group. The comparative focus of this case study, while adding additional layers of complexity to the data-set, provided an essential analytical tool in developing insights into the phenomenon of trial recruitment. Multiperspective interviewing from both sides of the recruitment exchange enabled a more nuanced and holistic understanding of trial recruitment than would have been achieved if only one side of the exchange had been explored. A pluralistic approach to analysis was able to highlight the contradictory, labile nature of people making sense of their social world, holding multiple positions and attitudes at one time. A purely conceptual or thematic analysis of recruitment might have failed to capture the personal, dynamic, situated experience of recruitment.

While a strength of this case study was the use of qualitative interviews, which ensured aspects of recruitment important to informants were included, a reliance on retrospective interviewing did not prove particularly conducive to eliciting the youngest participants' experiences of research. Parents in this study indicated that they had engaged with their child about clinical research from a young age but it was unclear how these children viewed this involvement since their accounts were significantly less detailed. Ethnographic studies which include observations of recruitment consultations and follow families through their trial experience from the point that a trial is first raised could be a way to access young children's trial experiences. This method would counter the limitations of the present case study design and enable a child to share their view in real-time rather than having to rely on cognitive abilities to recollect trial experiences.

My reliance on third party sampling, involving various levels of gate-keeping, must also be considered, as it is likely to have influenced who participated in the

interviews. Several CF centres declined for unclear reasons, and the recruitment process at each CF centre was entirely dependent on who the practitioners chose to approach. While I aimed to sample purposively to access a broad range of views, including those who had declined clinical trials, the final sample was weighted towards individuals with a more positive disposition to research. Furthermore, many parents within this sample spoke about initiating a form of moral training with their children and were also committed to negotiating their child's involvement in research discussions and indeed in this study.

Several practitioners declined to participate and those who did participate, for the most part, had a positive attitude towards clinical research, while acknowledging that other colleagues held less positive views. Therefore, it is possible that my findings over-represent the views of individuals with a positive leaning towards clinical research. Despite this, the study did contain numerous informants who were less encouraging about clinical research and several patients and families had declined clinical research in the past including some that had declined all invitations. Overall this case study comprised a large, rich, triangulated data set based on informants who were drawn from ten CF centres across seven regions in the U.K. Therefore I believe that this sample provided enough heterogeneity to assume these findings will have relevance to the broader CF context. Furthermore, the findings of this case study resulted in the advancement of an early effort to develop a conceptual framework, able to characterise how individuals make sense of their decision to engage with clinical research which included rational, social and psycho-ethical dimensions.

Nonetheless, the potential transferability of the study findings to other health contexts must be carefully considered in relation to the specifics of the CF

community. CF comprises a distinct chronic, life-limiting condition. It is typically diagnosed at birth, which gives rise to intensive health care relationships that span an individual's life. While the symptoms of cystic fibrosis can vary greatly from one individual to another, it typically comprises a multi-system disorder often affecting the lungs and pancreas, eventually resulting in life-threatening complications. However, due to advancements in treatments and knowledge made through research, the outlook and overall quality of life for individuals with CF has improved considerably. One important development has arisen in relation to infection control guidelines. Consequently, patients are advised not to meet face-to-face with other people with CF due to the serious health risks associated with cross infection (CF Trust, 2017). As a result of these guidelines, social support within the CF community offers special challenges for patients, families and practitioners. Therefore, a CF patient, taking part in research may endorse being part of a particular community in ways that are different compared to other patient groups.

Trusting clinical relationships are viewed by patients, families and practitioners as integral to successful CF care and these trusting relationships often extend to the research context. Many CF patients and families have also witnessed first-hand the developments in CF treatments made though research and remain hopeful for further improvements both for themselves and other people with CF. Moreover, the serious health risks associated with cross-infection mean that social support within the CF community largely exists virtually via social media platforms or through correspondence. Consequently, it is conceivable that within this particular health context the constructs of hope, trust and sense of responsibility are more pronounced for patients, families and practitioners, compared to other contexts, and particularly compared to acute or comparatively minor health situations. However, an important strength of this study was that not only did it bring into view key

constructs used to make sense of recruitment it also provided insights into the potential vulnerabilities in this act of making sense. The ethical concern most widely cited in the literature, that of patients sacrificing themselves for the benefit of future patients, was unfounded. Informants were not passive research subjects who were forfeiting their personal interests. Rather, they actively and consciously engaged in making sense of their research invitation, in line with their personal interests. Nonetheless, vulnerabilities were evident around hope, trust and duty, where high hopes could lead to disappointment, trust could turn to acquiescence and responsibility could lead to obligation.

The particular case of CF also captured a diverse range of trial and research experiences across an individual's life course, including 'run of the mill' antibiotic trials to revolutionary 'wonder drug trials'. Furthermore, situating these findings within the qualitative literature, particularly studies involving long-term conditions (including various types of cancer) suggests the key discourses and constructs developed from this study resonate with and unite existing evidence (e.g. Hallowell et al 2016; Cox & McDonald, 2013; Locock & Smith, 2011;McCann et al., 2010; Dixon-Woods & Tarrant, 2008; Madsen et al, 2007). Nonetheless further research is needed to establish the extent this conceptual framework is transferable to other health contexts and the priority placed on these key discourses and in particular how hope, trust and sense of a moral responsibility feature in other contexts.

In summary as an interpretive endeavour, I accepted that my account of recruitment did not represent an external reality but rather my goal was to use CF as a case study to construct a clearer picture of the phenomenon, to further empirical and conceptual understanding of the process. From a constructionist position, I took a

critical stance towards taken-for-granted knowledge and current discourses on recruitment, with my overall aim of informing understanding from insights gained from individuals with direct experience of the process. An idealised view of recruitment may exist within regulatory and ethical discourses; this case study draws attention to the importance of viewing recruitment as a social process and the requirement for knowledge of trial recruitment to be informed by the social actions of those involved.

8.6 Future Research

While a person's disposition to live in hope is often equated with the human 'drive to survive' and have 'something to live for' (Martin, 2014: Bruhn, 1984), the construct of hope in the context of clinical trials would benefit from further investigation. These findings suggest that high hope, rather than representing a therapeutic misconception or misunderstanding, were tangible benefits of trial participation satisfying distinct psychological needs of patients and families. Further exploration into the therapeutic value of hope in this context, combined with research examining the psychological impact of participating in research, may be important to ensure that potential participants are adequately supported throughout the research process.

This research also provided important insights into vulnerabilities which may occur during the recruitment process. Further exploration is needed into how best to help practitioners understand and respond to these vulnerabilities. While the study provided insights into the significance of the interpersonal context of recruitment. Further research is needed on communication practices that facilitate or compromise interpretation and decision-making in this context with the goal of

developing a clearer understanding of 'optimal messaging and communication processes' during recruitment (Thorne et al., 2013).

Within the child context, if parents are viewing assent as a form of moral training, further research may be necessary to understand how children perceive this moral education. Further exploration of parents' and children's views of a family-based model of consent and approaches which rely on the consent of competent children would also help to develop an understanding of how best to support families in their engagement with clinical research.

Evidence from this study and existing evidence indicates that the role of a 'recruiter' has the potential to be both emotionally and intellectually demanding (Lawton et al. 2015; Donovan et al. 2014). Consequently, future research, examining the emotional and psychological demands of recruiting patients to clinical trials is essential to ensure the development of ways to support the role of 'responsible researcher' in an ever-changing research environment.

These findings also suggest there may be potential to explore personal perceptions of fairness in the context of trial recruitment, within the framework of empirical ethics, a practical methodology which has been developed to integrate ethical theory with data from the social sciences (Frith, 2012; Borry et al., 2005). Empirical ethics is a significant move in bioethics to ensure ethical principles are informed by people's moral beliefs and to prevent ethical theory from being too abstracted or dogmatic (de Vries et al., 2011).

In the context of clinical trials, two aspects of the principle of justice or 'fairness' have been identified as relevant to the research process - fair outcomes and fair

process (Tilburt, 2007; Powers, 1998). Fair outcomes refer to either equal distribution of benefits and burdens of research, and fair process refers to the conditions under which individuals are selected and recruited to a study (Tilburt et al., 2007). While regulatory bodies may assume a fair process to recruitment is achieved by following the customary procedures of informed consent, my findings suggest that people's beliefs about recruitment extended beyond the view of autonomy embraced by the doctrine of informed consent reflecting a wider ethical framework. Rather these findings suggest that people's belief about their engagement with clinical research centred on personal perceptions of fairness. These perceptions included whether they felt the approach was reasonable, the risks were justifiable or whether they believed they had moral responsibility or duty '*to do their bit*' in the practice of research.

Despite the principle of justice and fairness being considered integral to the research process (Emanuel et al., 2000; Powers, 1998), people's actual moral beliefs about the perceptions of fairness in the context of clinical research have not been examined in a framework of empirical ethics. Owing to the increasing curative potentials of developing biotechnologies, understanding personal perceptions of fairness may become all the more significant for research regulators. An empirical ethical analysis on this dataset in the future or similar qualitative evidence has the potential to extend our understanding of the fair process in clinical research beyond informed consent to one that is informed by patients' perspectives.

8.7 Conclusion

How we understand the phenomenon of trial recruitment depends on how the tensions and uncertainties inherent in clinical trials are managed and by whom. Equally, how 'successful' recruitment is defined, depends upon whose interpretations this definition is based. Within this study, my aim was to inform our understanding of recruitment by accessing the perspectives of the individuals directly involved. The findings of this study support the view that the 'desire for experimental participation' is a legitimate interest of patients, particularly in the context of uncertain health (Feenberg, 1992).

Informants' motivations to participate stemmed from a basic appeal to fairness which was underpinned by an acceptance of research as a 'normative ideal' or moral responsibility and something which 'gives people hope' (Weisfield, et al., 2012; Fry, 2008; Harris, 2005). Viewing research as a form of duty and a source of hope was heightened within the context of a serious incurable condition in which clinical research has lead to significant increases in life-expectancy and where there are a limited number of potential participants. Nevertheless, while an informant's acceptance of the value and necessity of clinical research was at the heart of their construction of a fair offer, complexity arose for potential participants when negotiating the space between what is '*something good'* and a personal reticence about the uncertainty inherent in clinical trials.

These findings confirm the value of understanding and appreciating the complexity of an individual's perceptions and interpretations of trial recruitment - a complexity that is mirrored in the literature, which indicates a 'mixed and uncertain picture', containing 'hidden challenges' (Lawton et al. 2015; Donovan et al. 2014; Ulrich et al.,

2012). These findings indicate that trial recruitment is a complex social phenomenon involving 'a series of purposive and coincidental events, some situational, some intrapersonal and some interpersonal, all of which are embedded in a real-life context' (Stake, 2005).

While the accrual and protection discourse is essential to ensuring the scientific and ethical integrity of clinical research is upheld, findings from this study indicate that personal meaning was at the heart of a fair research offer. Individuals and families approached about trials wanted to be part of something of value and to be valued, engaging in what they believe is a worthwhile collaborative endeavour. The findings have implications for understanding recruitment and raise questions about the appropriateness of generic checklists and guidelines for enhancing and supporting the recruitment process. With continued research efforts, an increasingly rich holistic picture of recruitment is being achieved in which the subtleties and overarching dimensions of this challenging phenomenon can be better understood and supported appropriately. Deciding to take part in a clinical trial was constructed as something '*really personal'*, in which individuals drew upon elements from social, rational and psycho-ethical discourses to make sense of this unusual junction where science and health care meet.

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APPENDIX

Appendix 1: Examples of electronic searches of databases 350
Appendix 2: Children's Information Leaflet 354
Appendix 3: Topic Guide for Interviewing Parents: 358
Appendix 4: Transcription notation and identification codes 364
Appendix 5: Field Notes 368
Appendix 6: Case Summary 374
Appendix 7: Vignette describing RCT 378

Appendix 1: Examples of electronic searches of databases

Database: Medline

#	Search	Comments	Results
1	exp clinical trial/ or exp clinical trial, phase i/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or exp controlled clinical trial/ or exp randomized controlled trial/	Searched as Medical Subject Heading (MeSH) term (Medline is manually indexed with MeSH terms which can be used as a thesaurus to facilitate searching Clinical trial searched as as publication type, i.e. reports of a specific clinical trial Definition exploded i.e. results retrieved using the selected term and all of its more specific terms.	792867
2	exp clinical trials as topic/ or exp clinical trials, phase i as topic/ or exp clinical trials, phase ii as topic/ or exp clinical trials, phase iii as topic/ or exp clinical trials, phase iv as topic/ or exp controlled clinical trials as topic/ or exp feasibility studies/ or exp human experimentation/	Searched as MeSH term: Clinical trial as topic i.e. for general design, methodology, economics, etc. of clinical trials. Definition exploded	348856
3	exp Patient Selection/ or trial recruitment.mp.	Patient selection searched as MeSH term and trial recruitment searched as default keyword search in Ovid [multi-purpose (.mp)] set of fields includes - Original Title, Abstract, and Subject Heading. Definition exploded	50635
4	('randomi*ed controlled trial*' RCT or 'clinical trial*' or 'trial*'OR 'controlled trial*').mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	Keywords searched as free text words	807048
5	exp Qualitative Research/ or qualitative.mp.	Searched as MeSH term and default keyword search in Ovid. Definition exploded	117764
6	Interview/ or interview*.mp.	Searched as default keyword search in Ovid	237499
7	exp Nursing Methodology Research/ or constant comparative.mp.	Nursing Methodology Research searched as MeSH term. Definition exploded. Constant comparative searched as keyword search in Ovid.	16751
8	grounded theory.mp.	Searched as keyword search in Ovid.	5333
9	narrative.mp. or exp Personal Narratives/ or exp Physician-Patient Relations/	Personal Narratives and Physician-Patient Relations searched as MeSH term. Definitions exploded. Narrative searched as keyword search in Ovid.	73800
10	ethnography.mp. or Anthropology,	Anthropology, Cultural searched as	5474

	Cultural/	MeSH term. Ethnography searched as keyword search in Ovid.	
11	thematic analysis.mp.	Searched as keyword search in Ovid.	3421
12	attitudes.mp. or Attitude/	Searched as MeSH term and keyword search in Ovid.	157550
13	focus groups.mp. or Focus Groups/	Searched as MeSH term and keyword search in Ovid.	21213
14	(recruit* or enrol* or particip* or 'informed consent' or consent or declin*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	Keywords searched as free text words	1193659
15	(experienc* or understand* or concern* or view* or perspective* or opinion* or perce* or account* or reason* or motivat* or barrier*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	Keywords searched as free text words	3289832
16	1 or 2 or 3 or 4	Search for research focusing on some aspect of clinical trials	1183703
17	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	Filtering for qualitative research	527293
18	14 and 15 and 16 and 17	Filtering for qualitative research on recruitment to clinical trials	13099
19	"trial*".m_titl.	Search limited to articles containing trial in title, to focus search to qualitative research on trial recruitment	169359
20	18 and 19		2882

Summary: 850 duplicates, 1458 not related to trial recruitment, 574 imported into endnote

Appendix 2**: Children's Information Leaflet**

<<Details of Hospital Trust will be included here>>

CACE STUDY

Comparing **A**dults' and **C**hildren's **E**xperiences ***of being approached to take part in a clinical trial***

Children's Information Leaflet

MRC Hubs for Trials Methodology Research
North West Hub

Appendix 3: Topic Guide for Interviewing Parents:

Topic Guide for Interviewing Parents

This topic guide is only an outline of the possible questions and prompts that may be used and will be adapted according to the needs/preferences/experiences of each participant. The ordering of questions may vary according to the family's priorities.
There is no right or wrong answers to any of these questions I am interested in finding out your views and experiences of clinical trials and research in general.

General family background:
I will always give people the opportunity to provide any back ground information which they think may be helpful with regards to this study

General introduction to views/experiences of clinical trials:

1. If you wouldn't mind could you tell me a little bit about what the term clinical trial means to you/ what comes to mind when I mention the term clinical trial, have you heard this term before? Would you mind telling me a little bit about that?
2. Can I ask you to cast your mind back to when you first heard about the term clinical trial? Can you tell me a little bit about that?
3. Have your views towards clinical trials changed since you first heard about them. Can you tell me a little bit about that?
4. If not mentioned already ask if their child has *(yourself/other family member anyone you know)* ever been approached to take part in a clinical trial?

If yes, maybe

The following questions will depend on how long ago the patient family took part in a trial. It may be appropriate to focus on one particular trial e.g. the most recent or the trial the family choose to discuss?

Trial discussion

1. If you wouldn't mind, can I ask you to think about and talk me through (explain in your own words) how you came to be invited to take part in a clinical trial
2. When the idea of being in a clinical trial was first raised, what thoughts went through your mind?
3. Is there anything about the discussion(s) that sticks in your mind particularly?
4. Was there anything during the discussion(s) about trial that you weren't expecting?
5. Is there anything about how the trial was explained that could have been handled a bit differently?
6. Has your {child's name} been present when the subject of clinical trials has been raised, were they able to o take part in the discussion?
7. How did you find discussing the clinical with {child's name} present?
   Can you tell me a little bit about how your child was included in the discussion?
8. Who has generally brought up the subject of clinical trials? How do you think {name of recruiter} feel about clinical trials?

9. Did you know {name of recruiter} before he/she approached you about taking part in a clinical trial?
10. Did you or your child have any other discussions with the doctors/nurses/researchers about taking part in the clinical trial(s) while you were trying to decide?

Trial design:

1. In your own words, can you tell me a little bit about the trials your child has taken part in?
2. How did you feel about the different aspects of the trial?
   If necessary, prompt with key features of the trial only if they have previously been mentioned. How was it is decided what treatment was given? What did you think when (name of a consultant) told you about that?
   Probe on trial design e.g. randomisation, treatment preference, study duration, the number of additional appointments.
3. Did you think that over when you were making your decision? Can you tell me a little bit about that?
4. What other aspects did you consider when deciding?
5. Did you ask all of the questions that you wanted to about the trial? How did you feel {name of recruiter} dealt with your questions.
6. In general, how would you describe your experience of being approached to take part a clinical trial

The child:

Omit questions 1 – 5 if inappropriate:

1. I'd like to ask a few questions about {child's name} if that is OK. Did you discuss the trials with {child's name}?
2. What were his/her views?
3. Did she/he have any particular concerns? *Probe for whether they felt their concerns were the same or different to their concerns?*
4. Did you involve {child's name} or any other family member in the decision making at all? Can you tell me a little bit about this?
5. How do you think {child's name} feels about {trial name}/the decision that was made?
6. How did you feel his/her needs were dealt with when you were approached about clinical trials in the past, is there anything you would change?

Decision Making:

1. Can you tell me a little bit about how you made your decision whether to go into the trial or not
2. In making your decision about taking part in clinical trials what sort of things did you consider?
3. Was there anything specific that influenced your decision?

4. Was it something that you had to think about for long? How did you find deciding?
5. Was there anything you found particularly helpful in making up your mind? Was there anything you found unhelpful?
6. Apart from {name of recruiter} did you discuss it with anyone else? Can you tell me a little bit about that?
7. Did you ever feel under pressure when you were trying to make up your mind?
8. Did you feel that you were able to say no?
9. Did you feel you had enough time to think things over properly?
10. Now that a little time has passed, how do you feel about the decision you made?
11. Do you think that parents should always make that choice rather than the doctors? Can you tell me a little bit about why you feel that way?

The information sheet:

1. Did you receive an information leaflets about the clinical trial you have been approached about? Did you get a chance to look over it? What did you think of it?
2. Were they helpful/ unhelpful/ unclear/ was there anything you would change about the leaflets ?
3. Did you use the information sheet to help you to make your mind up about the study? {If so} did it help you at all?
4. In making your decision, what would you say was the most useful source of information?
5. How did you feel about the amount of information you received, both written information and the discussions you had with the trial staff.

Views on research:

1. In what type of research studies are you most interested in participating
2. What do you think about medical research involving people in general?
3. Has your experience with the clinical trials your child/yourself have taken part in influenced your views on research at all? In what way?

Amount and type of research (*This may need to come earlier and will depend on the informantsearly responses)*

1. Has your child been approached to take part in more than one trial, how many trials, can you tell me a little bit about each trial and what you decided?
2. How did the trials differ?
   May be appropriate to enquire about any other requests for research e.g. Survey, questionnaires, interview studies?
   What did you think about being asked to take part in this study (CACE study), have you ever taken part in other similar studies/ interview studies?
3. How do you feel about the number and frequency for requests to participate in research?

Views on research: (This may need to come earlier and will depend on the informants early responses)

1. Do you know how it gets decided how a piece of research is OK to do?
2. Prompt *research regulation, ethics committees, etc. Do you feel reassured that there is something in place?*
3. What motives do you think doctors have for planning and conducting clinical trials?
4. If I can ask you now to look into the future, maybe two or three years time. If the trial you/your child has taken part in, came into your mind, would there be things that you would be curious about? Would you want to know about the outcomes of the trial?
5. Is there anything else that you think is important to mention or anything you would like to ask me?

Appendix 4: Transcription notation and identification codes

Transcription notation and identification codes

The transcription notation for this study was adapted from Silverman (1993, 2006)

Code	Description
[ ]	Overlapping speech
(.)	Indicates a tiny pause, no more than a tenth of a second
(0.4.)	Indicates elapsed time in silence in tenths of a second
WORD	Capitals except at the beginnings of lines, indicate especially loud sounds relative to the surroundings
( )	Indicates transcribers inability to hear what was said
(word)	Indicates possible hearings
(( ))	Transcriber's transcription rather than actual transcriptions, e.g. of mood, context, gestures, people entering and leaving rooms etc.
-	An abrupt cut-off of the sound in progress
…	Speech trailing off

Study identification codes

Each participant that took part in this study was assigned a study identification code, which was used to label the audio files, transcribed interviews, socio-demographic forms and consent forms.

Each identifying code contained the following information and is displayed as such:

CF Centre/ paediatric or adult/ participant/ interview / age of patient

A	P	M	1	2

Therefore the identification code: **Ap-M1-2** refers to a research participant who is the first mother (M1) to be interviewed, who has of a 2 year old child attending a paediatric CF centre at Trust/hospital A at the time of the interview.

If the mother and father were interviewed together the identification code for this interview identification code would be: **Ap-M1-F1-2**

- M was used to identify the mother
- F was used to identify the father
- K was used the child or young person attending a paediatric CF centre
- A was used to identify a to identify patient attending an adult CF centre

Appendix 5: Field Notes

Field notes (Clare age 17)

Negotiating a meeting

The interview was arranged through communication with both Clare and M5 (Clare's mother). M5 encouraged direct liaison with Clare, regarding the time date and location of the interview, whilst implicitly indicating that she would like some involvement in the process. This was in part exhibited by only being provided with Clare's mother's mobile. Therefore, prior to arrival at the ward, I contacted Clare's mother who then contacted Clare to inform her of my arrival.

My perception of Clare's mother's actions was to fulfil the role of protector/ gatekeeper implicit/inherent in the role of parent, whilst simultaneously supporting and respecting Clare's autonomy and independence as a young person with legal rights etc. This carefully crafted involvement by M5 was mirrored during the interview process and was in part guided/instructed by Clare.

Negotiating recruitment in practice

My own process of recruitment provided me with insights into 'recruitment' per se. The idea of an 'infinity mirror' relating to studying the never-ending process which makes much human research possible, was put into my mind by a colleague. During my experience of approaching Clare for this study I was conscious of respecting the existing family dynamics, whilst also being aware of Clare's full legal autonomy regarding consent to research at the age of 17 and my role as a researcher in respecting this autonomy.

Interview setting

Clare had requested that I visit her on the ward for the interview as she had recently been admitted for a routine course of IV antibiotics. At age 17 Clare was still attending the Paediatric hospital in the region, the transitional process to adult services occurs somewhere between the age 16-18. During this admission, Clare stayed on the ward for IV treatments followed by an overnight stay. During the day Clare attended 6th form college where she was studying for her A levels. This appeared to be the normal routine for Clare during recent admissions. Clare explained that it was nearer for her to come from college back to

the hospital, rather than returning home and it was something to do while she was on the ward. Understandably for most people an interview in their own home was selected as it was considered the most convenient as *'another trip'* to the hospital outside routine clinic appointments was regarded as an inconvenience. For Clare however, at this time it was more convenient for her for me to visit her at the hospital

Clare had a single room so confidentiality was maintained. However I felt slight concern about my position, when nurses entered Clare's room to administer her treatment and I offered to leave the room, however Clare told me it was fine for me to stay. Clare seemed unconcerned by my presence during treatment, which I tentatively interpreted as Clare constructing medical interventions as a routine, everyday part of her daily life and something she did not want to be a hindrance to her activities of daily living. For things to be achieved, she had to effectively assimilate treatments (including hospital admissions) into her everyday life e.g. attending college while at hospital, taking part in a research interview whilst an inpatient in hospital. The admission appeared to be constructed by Clare as a routine almost 'mundane' part of her life, which contrasted with my conceptions of a hospital admission, involving heightened stress and an extraordinary event.

The interview

Clare appeared very relaxed and happy to get started with the interview once I had gone over the details of the study again. Half way through the interview Clare's mother knocked on the door and Clare gave her permission to enter. I briefly paused the recorder and introduced myself and Clare appeared to instruct her mum to the bathroom (attached to Clare's room only). I asked Clare if she would like her mother to join us in the interview but Clare said it was fine to continue. Halfway through the interview Clare's mother came out of the bathroom and sat on a chair next to Clare, where she remained as a silent observer for the remainder of the interview. Clare appeared relaxed and open throughout the interview and her manner appeared unaffected by the arrival of her mother. I anticipated that Clare's mother's arrival, and her decision to observe had been agreed beforehand. Clare's

mother appeared to strategically adopt a low profile under the discrete instruction of Clare. Again I interpreted this behaviour as fulfilling the parental role of protecting and monitoring whilst remaining sensitive and respectful to Clare's demonstration of independence and autonomy, but mum was there if Clare needed her.

Appendix 6: Case Summary

Case Summary

Mother (Tom <1yr)

Tom is 8 months old, the youngest child in the sample to have been approached directly about trial participation and Tom's mother acknowledged that she was only just getting used Tom's diagnosis. She indicated that she has never really thought about research before and was largely unfamiliar with the term clinical trial. TORPEDO trial was her first experience of being approached about a clinical trial. I questioned the influence of level of adjusted to a CF diagnosis and the possibility that having the trial raised at this early stage may have been too much to take in or deal with at this stage.

Comparison with other families re. adjusting to being a parent of a child with CF

- Alice's (3y) mother described Alice's father as '*still struggling to come to terms with it* (CF)'.
- The father of Harry (1yr) '*...you find out your child's got cystic fibrosis, it is like the end of the world and you go through a grieving process*. '

This parents period of adjust with her son's diagnosis combined with her lack of research experiences together appear to have contributed to her initial reticence about the trial. Comparable to parents she makes a distinction between the acceptability of research for herself and research for her child. This parent does not appear to be aversive to the concept of research per se, revealed by her agreement to talk with student Drs and her acknowledgement that 'she' would be happy to take part in research if it would help people. Nonetheless she is much more reticent about allowing Tom to take part in research while he is so young and unable to be involved in the decision-making process. She suggests 9 or 10 may be an appropriate age to involve children in research, when she perceived children are old enough to have a say themselves.

Three weeks prior to the trial being raised this parent referred to a traumatic blood test her son had had to endure. This experience was constructed as the main reason for this parent's decision to decline the trial, as she did not want to risk Tom being allocated to the IV arm of

the trial. Tom's mother appeared clear about the randomised nature of treatment allocation and indicated that she was aware that if she agreed to the trial she wouldn't have a choice with regards to which treatment Tom received. She did not allude to the concept of equipoise, nonetheless she mentioned that that she was aware Tom didn't have to have IVs (implying that she understood that there was no preferential treatment) then she would opt for the one that didn't involve needles. The only way to guarantee this was to decline the trial (as this involved not being allowed to choose) and opt for oral medication.

This mother described the approach for TORPEDO-CF comprising a telephone call from a Dr she had never met before and had been sent the information via the post, and then subsequently phoned to discuss her decision. She did not express any direct negativity about the approach, but when asked about ways to improve the approach, she stated that she would have preferred the trial to have been raised in person by somebody she knew from the CF team. She described feeling comfortable saying no, and she did not feel under any pressure when making the decision and she felt she had enough time to make her decision.

Tom's mother also constructed the invitation as akin to Tom 'being used as a guinea pig', despite the study comprising a phase IV trial of approved standard treatments for pseudomonas. Although she did not have any experience of either treatment she had a strong preference to avoid going into hospital and avoid any more '*traumatising Tom with needles and stuff*'. She also described how other family members had been supportive of her decision and had agreed with her view to avoid Tom being used like a guinea pig. In addition at the time of recruitment she could not see any direct or future benefits for Tom participating in the trial. However since the oral medication did not eradicate the infection, Tom has had to have IVs anyway and the line was fitted whilst Tom was under a general anaesthetic. M4 reflected on how participation in the trial might have resulted in the infection being treated 'better'. Nonetheless M4 implied discomfort with her proxy role while Tom does not have a voice and suggested it would be preferable to wait until Tom is older and he can have a say in the decision. She spoke of how making a proxy decision on behalf of her infant had the potential to result in self-blame if something happened.

Appendix 7: Vignette describing RCT

Description of RCT

Clinical trials are used to compare different treatments to see which one works best. Clinical trials are carried out because doctors are unsure which treatment works best. For example clinical trials may be used to compare whether treatment A or treatment B works best. Randomised Controlled T rials or RCTs for short, are the most widely used type of clinical trials.

If you were approached about a clinical trial, it would be up to you to decide whether or not to take part.

In a study with two treatment groups half (50%) of the people in the study would be given (Treatment A) and the other half would be given (Treatment B), so there would be a 50/50 chance of you getting either treatment group. If you were to agree to take part in an RCT, you would not be able to choose which treatment you get. You would be randomly allocated to one of two treatment groups. The decision of which of the two treatments you would receive would be made by chance (this is called 'randomisation').

If it were left to doctors or researchers to decide they might (consciously or unconsciously) put patients who were more likely to get better into a particular group. This would make the trial unreliable - no one would be able to tell if the new treatment really works.