

The Trial That Goes Wrong

Application of the model of organizational accidents to understanding the failure of clinical trials: Case study of a UK public sector-funded clinical trial of an investigational medicinal product

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Abstract

Successful clinical trials are essential to guide clinical practice, however, there is significant risk involved in ensuring the delivery of a successful clinical trial. The most common reason for randomized controlled trial failure in the UK is the inability to recruit in an adequate and timely manner. Trials that end prematurely without reaching their intended goals raise considerable ethical and financial concerns.

This study uses a single multisite randomized controlled clinical trial of an investigational medical product, which was closed early, as a case study setting to explore the circumstances around trial failure.

Aims were to explore the reasons for trial failure, and in the context of the literature, learn lessons that could help to reduce the risk of failure in future studies.

A systematic review of the literature was undertaken in order to examine causes of poor trial recruitment, and to validate the methods used as part of the assessment of the case study trial.

I explored experiences and perceptions of individuals from stakeholder groups about the failure of this trial, analysed the data and mapped the results to the Model of Organisational Accidents and the Team error taxonomy. This is the first application of Reason's model of organizational accidents within a trial management context

A qualitative design was used, using semi structured interviews with a purposive sample of individuals representative across the trial stakeholder groups. Interviews

were conducted, fully recorded and transcribed, then analysed using frameworks derived from the risk management literature to provide a descriptive framework for the context of the case study, and then a second body of theory was used to provide an explanatory framework in order to see links between the actions of individuals, groups and situations in order to better understand the reasons why this trial failed.

The case study trial had shortcomings in design, had setbacks in the planning phase, where there were significant delays in appointing staff and commissioning essential components of the trial. The study fell behind time, there was budgetary overspend and issues throughout the trial relating to poor communication between stakeholder groups.

All of the mistakes and lapses that occurred over the course of the study were avoidable, but the combination of inadequate experience, resources and motivational factors led to an atmosphere where mistakes were not identified or corrected due to factors relating to institutional hierarchy.

The case study showed how fallible decisions at a senior management level allowed line management deficiencies within a project team and an environment where mistakes, violations and unsafe acts could occur. The analysis shows how the whole organizational system contributes to causal pathways associated with project failure, taking account of the culture of an organization and issues such as 'excessive authority gradient'.

The study suggests the need to improve monitoring of clinical trials and their progress, and aiming future research towards how funders assess investigators and host institution infrastructure as fit to lead research projects. The future development of a robust risk assessment tool that can be applied to new research projects may be useful in preventing a similar situation in the future.

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1. Introduction

1.1 Background

In order to ensure the very best therapy and management of all clinical conditions, testing treatments and monitoring response is an essential component of an evolving and improving healthcare system. Successful clinical trials are essential to guide clinical practice and are requested repeatedly and persuasively in the literature .

Clinical trials are historically defined as deliberate experiments designed to assess the value of therapeutic procedures for patients (3) and help to determine best practice. Randomized controlled trials (RCTs) are considered to be a robust way of evaluating clinical interventions (4), primarily because of the main principles of design, which include the comparison of the outcome of the patient randomly allocated to two or more clinical interventions in order to ensure similarity of characteristics at the start of the comparison (5). The very first published randomized trial is credited to Austin Bradford Hill in 1948 – where in an MRC funded trial of streptomycin in the treatment of tuberculosis, random numbers were used to assign trial participants, ensuring unbiased comparison groups (6).

The conduct of clinical research has the potential to provide significant health benefits to a society: through the introduction of research infrastructure into a health system (7); research participation may bring benefits to individuals who agree to participate in research (8), and through the health gain of the application of medical advances to society as a whole (9). Research participation has been shown to lead to considerable benefits to societal economy, and through ongoing commercial

development, all of which justify an ongoing investment in health and biomedical research (10).

Modern clinical trials are often highly complex, with high levels of methodological sophistication, complicated regulatory bureaucracy, and quality standards that need to be maintained at a high level. A successful trial answers a well formulated and worthy question and measures outcomes that are clinically and socially relevant, well defined, valid, reliable, sensitive to important change, and measured at appropriate times. The trial must be designed with appropriate methods and conducted so as to minimise bias and maximise statistical power and external validity (11).

Although randomized controlled trials are seen as the most rigorous way of determining whether a cause-effect relation exists between a treatment and outcome, and for assessing the cost effectiveness of a treatment, they are generally expensive and time consuming (12). Because of the significant investment of time, human and financial resources – added to the complex nature of RCTs, there is always significant risk involved in ensuring the delivery of a trial. Those trials that terminate prematurely without reaching their intended goals raise considerable financial and ethical concerns (13).

1.1.1 Stages in the conduct of a clinical trial

Conducting a clinical trial in the UK from the starting point of getting an idea, or a hypothesis that a researcher feels is of importance to test, to completion and publication of results is a process that consists of a number of stages, each of which takes a certain amount of time (14).

The first stage is conception of the idea, this is the point at which a research need is identified and a hypothesis is conceived which then requires testing. The next stage is that of designing the clinical trial, establishing a method by which the hypothesis can be tested. This is done through putting together a study protocol that outlines the methods by which the trial will be conducted. Commonly it is at this stage that funding is also applied for in order to ensure financial backing and overall support from a funding body. Health research in the UK has a variety of funders and funding mechanisms, from public sector, charities and the health industries. The Wellcome Trust, Cancer Research UK and The British Heart Foundation are three of the largest individual charity funders. The Medical Research Council (MRC) and The National Institute of Health Research (NIHR) are some of the key funders in the public health sector (15).

After this stage permissions are sought. This involves making applications to regulatory bodies for approval in order to conduct the planned research, this will include application to an ethics committee, NHS research and development (R&D) and often other bodies, such as the Medicines and Healthcare products Regulatory Agency (MHRA) in order to ensure that the research that is planned is ethical and legal. Certain measures may be recommended in order to ensure safety for researchers and trial participants, such as regular evaluation of data that has been acquired during the course of the trial by a committee of people who are not directly involved in the trial that is being conducted in order to ensure that results are as expected, and, for example, no large differences are seen between the groups being examined, such as the treatment group on study medication having a significantly

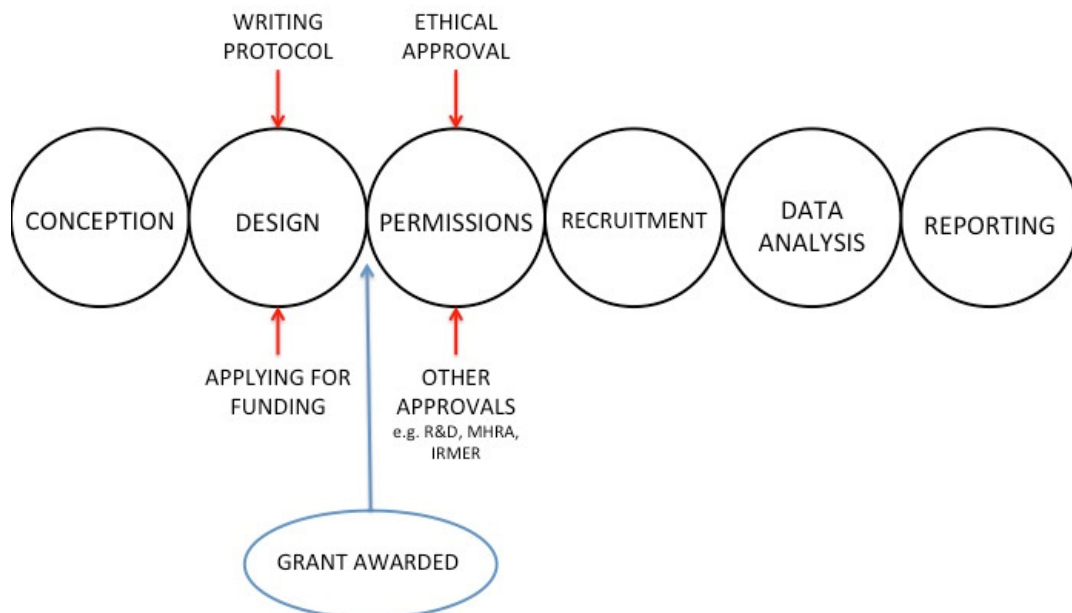
higher rate of mortality in comparison to the group receiving placebo. Approval from an ethics committee and their right to monitor research studies is stated within the Declaration of Helsinki; a statement of ethical principles for medical research involving humans (16).

Once permissions are granted, then recruitment of trial participants can commence, and data can start to be collected.

Following data acquisition, data analysis can then take place, in order to assess fully whether there is any significant findings, and whether the hypothesis being tested is supported or refuted by the trial findings.

The final stage of conducting a clinical research trial is that of reporting the results – this is essential, irrespective of whether the trial results support the hypothesis, refutes it, or are equivocal, responsible research practice dictates that all results should be published. According to the declaration of Helsinki

‘Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available (16)’



(R&D – Research and Development, MHRA – Medicines and Healthcare products Regulatory Agency, IRMER – Ionizing Radiation Medical Exposure Regulations)

Figure 1. Stages in the conduct of a clinical trial

1.1.2 Failure of Randomised Controlled Trials

RCTs are seen as an essential tool to inform clinical practice, and many funding agencies expect that the research to compare approaches to care should use a RCT unless there is good justification for an alternative approach (17). Recruitment to trials is often slower (18), and more difficult than expected, and it is not uncommon for trials to fail to reach their planned sample size within a projected timescale (19), within a planned budget (20). This can have an effect on the reliability of the results, and should the trial need to be extended, or the protocol amended, this can incur extra costs for the funder, and delay changes to clinical practice in the long term (21).

Some RCTs are flawed in their design, and in other cases, there are issues that emerge as the trial progresses (22). Unfortunately, many RCTs face difficulties, and some face delays and increased spending to the extent that further support from a funding body becomes unfeasible, and a trial is closed (23). The most frequent reason for a trial to fail and be closed early is difficulty in recruiting study participants (24, 25). It is likely that 50% of RCTs fail to recruit to target and that only 50% of those that successfully recruit do so in a timely manner (25).

1.2 The Research Journey and the Development of the Research Question and Objectives

The purpose of this section is to document the process through which the final research questions and objectives were developed.

My background is that of a physician. At the time of embarking on this medical doctorate, I had been working as a junior doctor for 5 years. I applied for a position in a university department as a clinical lecturer and research assistant – working as part of a new clinical trial, comparing the effects of two generic medications on a chronic disease population. I was appointed to the position and started work in June 2012. Soon afterwards I enrolled onto the medical doctorate programme, my doctoral supervisor was the Chief Investigator of the trial. I was accepted, and my MD began in November 2012.

As a research assistant, my responsibilities included working as part of the core trials team. As part of this, my duties included: screening study participants through reviewing test results and ‘case report forms’ and comparing these with inclusion and

exclusion criteria, entering data (such as blood test results and similar investigations) into a database, recording adverse events and following them up, and identifying and approaching prospective study participants that had been identified locally.

Alongside my trial duties I continued to do clinical work, which included regular outpatient clinics. I was also involved in 'marketing' of the clinical trial – as part of this I played a part in promotion of the trial, setting up presentations at meetings and conferences where prospective trial investigators would attend – in order to encourage their involvement as peripheral sites, and to answer questions and concerns about what was needed in order to participate in the trial, from my experience 'On the Front Line' of recruiting patients and identifying prospective participants in outpatient clinic.

In October 2012, senior management staff at the University were alerted by the trial funder that the trial was 'in difficulty'. It had failed to progress, and poor recruitment of both participants and other centres had caused considerable concern. At this point, day-to-day management of the trial was taken over by a professor from elsewhere in the research department. Unfortunately, despite efforts and an increased level of departmental support, the notice of closure was issued by the funder, and the trial closed on the 1st January 2013. Soon afterwards, the Chief Investigator of the trial, who was also my academic supervisor, left the employ of the University to take up an alternative post in another institution.

Following closure of the trial, I continued to see study participants (in order for all included participants to complete the study protocol and attend all required monitoring visits), and presented the findings based on the 87 patients that had been

included and randomized as poster presentations at conferences and meetings. My supervision had now changed to another professor within the department, and focus of my research turned towards looking into the reasons why this trial failed. This research was embarked upon with full support from the Chief Investigator of the trial.

My initial point of contact – and point of reference – was that of the Risk Management Department within the hospital trust. Through clinical experience and training I had learnt about Serious Incident assessment and ‘Never Events’ – a term used in healthcare that describes an unacceptable error ‘that should never happen’, examples that are commonly cited include wrong site surgery, or an unexpected death (26) (27). I spent time with this department in order to become familiar with how the hospital trust investigate errors that have occurred, and the methods that they use in order to identify areas that change can be made, and the errors prevented in the future. Through this, I became aware of ‘Root Cause Analysis’ (28) (29) and tools that are used in order to identify where problems have occurred, through working back and looking at the series of decisions that had been made, and the actions that had taken place in order to allow a catastrophic event to take place. The tool that was being used most regularly was one called the ‘5 Whys’ (30, 31) – it being well known as the most commonly taught approach to Root Cause Analysis in healthcare (32). I used the ‘5 Whys’ tool to inform a very simple set of questions that I used to guide the interviews that I conducted with the key stakeholders that were involved in the trial.

With the support of my new supervisor, I attended university courses in order to understand some of the theory behind qualitative research, and how I would go about obtaining the data required, and analyse the results. I was put in touch with a GP that had completed an MD in qualitative research and complexity theory, and we had a series of meetings and supervision sessions, wherein we coded transcripts together and used concepts of grounded theory to examine for emergent themes. We also addressed the questionnaire, and revised the structure of questions. Healthcare organisations are complex, and historically complexity theory has been used to study different aspects of healthcare including management (33), nursing and decision making (34). We also spent time discussing social theory relating to complex systems, and I spent time with the Dean of the Business School at the University of Hull in order to gain a little insight about the interactions in complex systems – from a business theory point of view. It was during this period that my supervisor changed once more, to Professor Sheldon, my current supervisor.

In the NHS at this time, there had been some recognition of the fact that errors and medical adverse events were occurring in a complex environment. There were parallels being drawn between healthcare and the aviation industry (35), describing similarities in the conditions that both pilots and doctors work in, and that in both environments there had been issues with hierarchy and teamwork, where team error can lead to the occurrence of adverse events. The aspect of this model that had most resonance with me is that there are always a number of situational, environmental and organizational factors that could influence an outcome, as well as the characteristics of the team – how well the team is communicating, fatigue and factors associated with the workload they are experiencing. I felt that there were certainly

parallels to be drawn between the complex systems being described in the literature – that of cockpits in aeroplanes, NHS operating theatres, and my particular case study – that of a randomized clinical trial.

I decided to use framework method of analysis for the data, as it provided a systematic model for managing and mapping the data that was being obtained, and a way of constant comparison within and between cases (36) – in order to do this I attended a series of courses at NatCen Social Research Institute in London. I examined the data that I had obtained through interviews, and using the documents and journal notes that I had made throughout the data-gathering phase of my research. Through this I was able to develop a greater understanding of the challenges that were faced by the trials team, and characterize particular incidents and conditions that may in part have contributed to the failure of the trial – however, I did not feel that I had managed to understand why the trial failed.

It was at this time that I revisited everything – looking at the raw data, and looked to the literature. I visited a clinical trials unit in Aberdeen, and spent some time trying to understand what measures a well established trials unit undertake to prevent trial failure. I presented the case study trial to the team there, and started to understand about how special this trial failure was – a lot of things went wrong – and so it potentially illustrates many of the causes. Events and factors to do with the research environment and organizational culture that in isolation would not be that unusual, but in the case of this trial combined together to form a ‘perfect storm’ such that it failed. The culture of the organization, the institutional hierarchy, and the inexperience of the core team meant that mistakes continued to be made. There were

delays – differences in predicted timescales for the appointment of staff, establishment of ethics permissions etc – which again, in isolation would not necessarily have caused trial failure, but in this complex system, where the conditions were perfect, and all variables aligned, the accident and trial failure occurred.

The work of James Reason and his ‘Swiss Cheese’ model and model of organizational accidents takes account of many of these factors, and it was at this point that I revisited the raw data, coded it to a planned framework with themes that were derived from the Clinical Trials Risk Management literature (11), and aspects of the Good Clinical Practice Guideline (37). I then mapped it to the Model of Organisational Accidents (38) and Team Error (39) taxonomy. This helped me to come closer to developing an understanding of what causes the failure of clinical trials – using this very unique trial as an example.

When developing the original research question, and trying to summarise the objectives, I remember when I embarked on this research, and how so many people that had been involved and invested in this trial expressed their frustration – exasperated after investing their time and energy in the project, and feeling that despite best efforts, it had failed. Individuals blamed themselves, or other individuals. ‘The System’ and outdated bureaucracy in the funding organization, the sponsor organisations, and the healthcare system were blamed. I felt that it was important to make sense of what had happened, and how a clinical trial that was so important – addressing a question that was seen as important enough to attract an enormous amount of public funding, and involve a wide range of expert individuals

with a wealth of experience and knowledge could have failed. Throughout this research I was very well supported by all the organisations and individuals involved – the question of why this trial failed captured a lot of people’s imagination, and felt like an important question that needed to be addressed such that if a similar trial was to come along in the future, the organisations and individuals involved could feel cognizant of risks, and through this, empowered to take appropriate action before an adverse event, or trial closure, occurred.

A further reflexive piece can be found in the discussion (Chapter 8) – where focus is on the epistemological foundation of the research, and relation to participants.

1.3 The Research Question and Objectives

The overarching aim of this research is to better understand why clinical trials fail, through examination of literature around the subject and using a single case study of the failure of a large publicly funded randomized controlled clinical trial of an investigational medical product.

In order to effectively answer the research question of why this clinical trial failed, the following objectives will need to be met:

1. A literature review – looking specifically at studies that have examined trials in difficulty. Using this information to inform the validity of methods used, and to look at the themes emerging from the literature.
2. Collecting data from observations, documents and interviews with stakeholders involved with the trial in order to build a picture of what happened in the trial.

3. To explore the impact of design features, planning measures and implementation factors that might be critical to the success of a trial.
4. To analyse the data obtained, and map the results to the Model of Organisational Accidents and the Team Error taxonomy.

1.4 The Structure of the Thesis

The failure of clinical trials due to under-recruitment is a frequent and costly occurrence, which should be avoided where possible. The clinical trial that I explore as part of this thesis was closed due to under-recruitment – this thesis examines the series of events that led to this closure and puts it in context of the literature.

The argument presented in this thesis is that, in order to better understand the failure of clinical trials, approaches such as those used to analyse and understand failures in other areas (such as serious incidents in health care) are fruitful and that a systems approach is necessary. In the central case study of this thesis, I apply a theoretical model derived from social psychology, human factors and cognitive science to better understand the failure of a large public sector clinical trial. The theoretical model predicts that project failure has linked systemic rather than isolated causes, which go to the top of an organization and its attitude to risk management. In applying this model to my case study, my key finding is that under-recruitment of participants is a risk that is related to how trials are designed and managed within a wider infrastructure. This finding will allow organisations hosting trials to better understand and manage the associated risks in the future.

In Chapter 2, I report a systematic review of qualitative research studies of under-recruiting trials. I use this to summarise previous findings, locate my own work in a research tradition and inform the methods used in the thesis.

Chapter 3 describes the case study trial. The conduct and reporting of similar trials in the same disease population is discussed in an attempt to describe the research environment and tradition of similar research trials that had been previously conducted. I present timelines, describing the main events in the case study trial, from grant award to trial closure, and how they related to the failure of its implementation.

Chapter 4 discusses the theoretical overview and approach to the case study – bringing in theories derived from the literature that will use as part of the framework coding structure, and those that are used for the analysis and mapping and interpretation of the results. I describe theories that are derived from the clinical trials risk management literature (Robinson) (11), and the ethical and legal framework for good practice (ICH-GCP) that will form the basis of the deductive approach to analysis and inform themes that are described in the results section. I also describe the Model of Organisational Accidents (38)– which will be used as part of the analytical and mapping process – described in the results section.

Chapter 5 constitutes a general discussion around qualitative methodology and discusses qualitative methods in general terms, and the justification of using a case study approach, interviews and documentary analysis for the purposes of my research exploring why this large clinical trial failed.

Chapter 6 describes the methods used in the Interview Study and data collection – development of a series of interview questions based on the ‘5 Whys’ tool, description of the interview settings and participants. It also describes my approach to data analysis – which was initially performed in an inductive way, using principles of grounded theory. I describe how I made the decision to revisit the literature and to change my approach in order to better answer the research question, using approaches (derived from the theories described in chapter 4) that have never been used for this purpose in previous studies of failed trials.

Chapter 7 revisits the raw data, using framework analysis again, but using themes that are derived from the clinical trials risk management literature. Results from this are then mapped to the ‘Model of Organisational Accidents’ described in the work by James Reason (38). This is then used to describe factors – based on the Human Error Model (40) that contributed to the failure of the clinical trial, by using techniques that have historically been used to investigate failures in other areas such as aviation disasters, and more recently, ‘serious incidents’ in healthcare (35, 41-44).

Chapter 8 is the discussion chapter, where there is the discussion of the findings in the context of existing literature used to gain a deeper understanding of why clinical trials fail to succeed, based on the case study examined, and the views of those professionals that were interviewed through this process. The implications of this study will also be discussed in the context of existing literature and current practice, and the working culture and environment that these participants are in. The chapter will include a discussion of the strengths and weaknesses of the study, and also

consider the trial case study once more – asking the question of whether there are steps that could have been taken to prevent another case such as this. There will also be a significant reflexive section.

The thesis will finish with a conclusion chapter, where the key findings will be summarized, and implications of the results will be discussed.

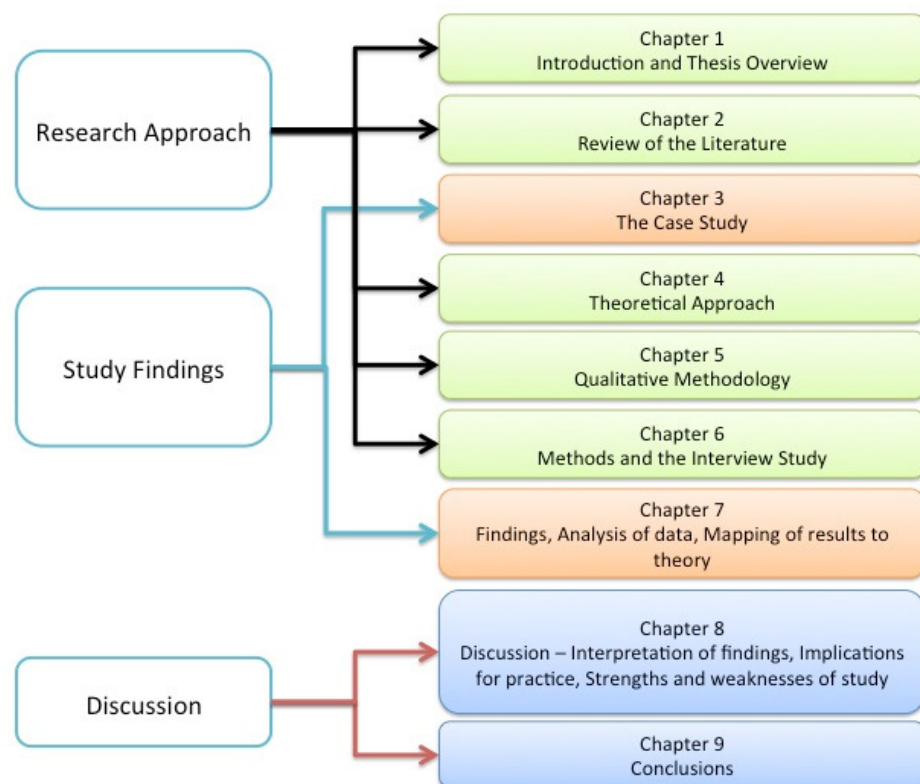


Figure 2. Thesis Structure

2. Literature Review

2.1 Introduction

2.1.1 Recruitment to randomized controlled trials

Randomised controlled trials (RCTs) are incredibly important in the establishment of safe and effective interventions in healthcare. They are widely accepted to be the gold standard in the evaluation of an intervention, as they are the most rigorous way of determining whether a cause-effect relation exists between a treatment and outcome, and for assessing the effectiveness of a treatment. (12)

Recruitment to RCTs is challenging and involves significant investment of time and financial resource. A successful outcome, and answer to the trial question depends crucially on the participation of volunteers as trial participants. Trials that end prematurely without meeting planned goals and endpoints raise a number of issues – firstly, issues with the financial waste (45) – resources that could have supported other endeavours, ethical issues associated with exposing participants to the potential harms of taking part in the trial and then failing to use their contribution (46), and finally, scientific issues – a delay or inability to answer an important scientific question – leading to delays in the implementation of a potentially beneficial treatment, or continuation of a level of uncertainty regarding treatment efficacy (47) – particularly important as the research question had been deemed important enough to be awarded permissions and, in most cases, financial support. This is compounded

by the fact that data from trials that end prematurely are less likely to be put in the public domain (48, 49).

Failure to enroll an adequate number of trial participants is a common reason for delays, and premature termination of an RCT. A retrospective analysis of 419 US National Cancer Institute sponsored oncology trials reported that 71% of phase 3 trials closed without meeting 100% of their accrual goals between June 2000 and December 2004 (50). In reviews of clinical trials registries – out of 7776 US oncology trials registered between 2005 and 2011 – 20% had failed to complete (terminated early) with the most common reason being “poor accrual” (39%), this is similar to results found in a survey of the US ClinicalTrials.gov registry of terminated clinical trials published in 2015 (Poor accrual responsible in 57% of cases) (13) and in cardiovascular trials registered in the US, where out of 6279 trials, 10.9% were terminated prematurely, with lower than expected recruitment cited as the main reason in 4% (51).

There is a need to find out why trials fail to recruit - a review of large UK-based multi-centre trials funded by the Health Technology Assessment (HTA) and Medical Research Council (MRC) in 2007 reports that 45% required an extension (20). It is in the interests of organisations that fund trials, and the general public, that recruitment plans provided by trial teams are as accurate as possible in order to avoid the financial, clinical and ethical costs of trial extensions or failures. In order to be able to better predict whether recruitment of sufficient eligible participants is possible for an RCT, an important starting point would be an examination of RCTs that have been affected by poor recruitment, or have been closed, and what the views and

experiences of the recruiters involved can add in order to reduce the risks of trial failure.

2.1.2 Objectives

The objective of this literature review is to examine evaluations that have taken place of trials that have failed to recruit sufficient numbers of participants, have been highlighted as trials with ‘issues’ with recruitment, and at high risk of not achieving recruitment targets, or trials that have been closed due to inadequate recruitment. As a secondary objective, the methods used to research failure to recruit will also be explored.

2.2 Literature review methods

The PRISMA statement of reporting guidelines for systematic reviews (52) was used to inform the structure of this literature review, and points addressed as appropriate, to ensure quality of reporting.

This review of the literature seeks to evaluate both qualitative research, and survey-based research undertaken to explore the experiences and views of researchers’ difficulties encountered with recruitment to clinical trials.

Two bases will be used to order findings, to identify themes in the literature and aid analysis. First, key concepts suggested by previous reviews of cohorts of trials that have explored factors that have influenced recruitment and have characterized these factors that are likely to affect recruitment. Second, previous reviews of the literature

that report difficulties in recruiting to RCTs – these will be identified through the course of the literature searches and reported as part of the analysis and synthesis of the results.

2.2.1 Criteria for inclusion

2.2.1.1 Study types and participant

The studies examined were those that investigated trials that failed to recruit the planned number of participants, and the reasons why. Those that considered the views of clinicians, researchers and recruitment sites (any individual or group of individuals responsible for recruiting trial participants) were included.

Studies that looked specifically at trials that failed to recruit, had issues with recruitment (such as delays or a paucity of eligible participants) or had closed due to insufficient recruitment were included. Studies that were included were those that either interviewed the study population (and data was analysed using qualitative methods) or surveyed the population using methods such as questionnaires.

In addition to this, articles that examined the difficulties in recruiting to RCTs – in the form of reviews of the literature, and reviews of cohorts of trials were also searched for, and helped to form the basis of the themes that were used for analysis of the literature review.

2.2.1.2 Types of intervention

No specific trials intervention was examined in this review – rather, studies that looked at reasons why specific trials failed to recruit, both prospective and retrospective studies were considered.

2.2.1.3 Outcome measure

Primary: Reasons why the trial under examination failed to recruit as expected.

2.2.2 Identification of studies

Systematic searches were carried out for the period to 8th February 2017 in the following databases: Cochrane Library, Ovid MEDLINE 1948-February 2017, Ovid EMBASE 1974-February 2017, PubMed and CINAHL.

Search strategy is available as an appendix (Appendix 1 pp308), and was developed in collaboration with Mark Clowes, Librarian at The School of Health and Related Research at Sheffield University (SchARR). UK and US spelling was used for all searching, and there were no limitations set for language or years searched.

In addition to database searching, hand searching was performed through key journals – BMC methodology (2001 to present) and Trials (2006 to present).

Handsearching is a valuable tool, and continues to have a valid role in identifying suitable material for inclusion in reviews (53).

In addition to this – previous literature reviews, and studies of cohorts of trials that looked at difficulties of recruiting to RCTs were collated and informed development of the themes used for synthesis. These were identified through the screening and inclusion process.

2.2.3 Selection of studies

Criteria for selection for suitable studies are defined and shown below:

Nature of study

- Qualitative data collected, or Survey (Questionnaire) data collected
- Clear, well defined methods for data collection
- Methods of data analysis well defined
- Number of participants defined (Number of questionnaire/survey respondents or number of individuals interviewed)

Attributes of RCT under examination

- Trial that had failed to recruit to target, OR had documented issues with slow recruitment, OR trial closed due to insufficient recruitment

Study population

- Individuals or groups of individuals responsible for recruiting trial participants

Box 1 Criteria for study inclusion

2.2.4 Data Extraction

Data extraction of included studies was carried out using a specific proforma that was designed for this review and data set. Data were extracted on: Trial setting, RCT details, Population included, Sampling methods, Type of study, Method of data collection, Data analysis methods, Main themes examined, and recruitment issues identified.

In addition, data was collected in order to allow the risk of bias in each study to be determined.

2.2.5 Methods for analysis – derivation of themes

As part of the literature searches performed above, literature reviews were identified that examined the difficulties in recruiting to RCTs. Only two of these included any

qualitative data, and in both reviews that included qualitative data, these made up a very small proportion of the studies examined.

Previous reviews of the literature have attempted to describe barriers to participant recruitment, and these are discussed below. In addition to this, a number of studies that have examined cohorts of trials are also discussed - these describe difficulties in recruiting to RCTs through examination of reports from completed trials and those that have been funded by certain funding bodies. Through examination of both of these sources, some overarching themes were identified. These informed the development of a thematic framework for the whole dataset. A thematic analysis allows clear identification of prominent themes, and a structured way of managing the data (54). The same themes were reviewed and compared when they occurred in different studies, and greater emphasis was given in the analysis towards themes that had a higher level of explanatory value rather than those that occurred most frequently (55).

2.2.6 Quality appraisal

Studies found vary by quality and it is important to appraise study quality so that it can be taken into account when taking stock of the knowledge base. Critical appraisal is the process of systematically examining research evidence to assess its validity, and relevance before using it to inform a decision (56, 57). Two tools were used to appraise the quality of included studies: CASP was used for qualitative studies, and the Critical appraisal of a survey tool was used to appraise survey studies.

Appraisal of the identified qualitative studies utilised the adapted version of the Critical Appraisal Skills Programme (CASP) checklist for qualitative studies (2).

This is a tool that has been widely used in the syntheses of qualitative studies and to inform decisions regarding the exclusion of poor-quality papers (58). The checklist consists of a series of ten questions that helps the reviewer to assess the rigor, credibility, and relevance of the study. A list of these questions is detailed below. An overall quality assessment of 'High', 'Medium' or 'Low' was assigned for the purposes of the tabulated results (CASP score was out of 10, a score of 0-3 was 'Low', 4-6 was 'Medium' and 7-10 was 'High'). A more in-depth table demonstrating the CASP quality assessment scoring for each study is available as table 2.

CASP appraisal tool (10 questions) (2)

- Was there a clear statement of the aims of the research?
- Is a qualitative methodology appropriate?
- Was the research design appropriate to address the aims of the research?
- Was the recruitment strategy appropriate to the aims of the research?
- Was the data collected in a way that addressed the research issue?
- Has the relationship between researcher and participants been adequately considered?
- Have ethical issues been taken into consideration?
- Was the data analysis sufficiently rigorous?
- Is there a clear statement of findings?
- How valuable is the research?

Box 1: CASP appraisal tool

Appraisal of the survey studies utilised the Centre for Evidence Based Management tool for 'Critical appraisal of a survey' (1) – this quality assessment rating is available in Table 4.

Box 2: Critical appraisal of a survey tool

Critical appraisal of a survey (12 questions) (1)

- Did the study address a clearly focussed question/issue?
- Is the research method (study design) appropriate for answering the research question?
- Is the method of selection of the subjects (employees, divisions, teams, organisations) clearly described?
- Could the way the sample was obtained introduce (selection) bias?
- Was the sample of subjects representative with regards to the population to which the findings will be referred?
- Was the sample size based on pre-study considerations of statistical power?
- Was a satisfactory response rate achieved?
- Are the measurements (questionnaires) likely to be valid and reliable?
- Was the statistical significance assessed?
- Are confidence intervals given for the main results?
- Could there be confounding factors that haven't been accounted for?
- Can the results be applied to your organization?

In a 'best case' scenario, a qualitative synthesis or primary study will achieve a positive assessment or score for each of the criteria against which it has been assessed according to the critical appraisal instrument used. For studies that fail to report sufficient information, or it is clear that the study is weak when matched against a certain criterion (e.g. because of a methodological flaw) a decision needs to be made about whether to include a study or not.

In the same way, it is essential to ensure that the quality of this case study research project that constitutes the main body of this thesis is similarly critically appraised using the same instruments that are used to assess the quality of those studies that have been incorporated into the review. Quality appraisal will be applied and explored further in the Discussion Chapter at the end of this thesis.

All studies that were selected for inclusion underwent quality appraisal using the tools above - the CASP appraisal tool was used to ensure that all qualitative interview studies that were included were of reasonable quality – each included study was appraised, and the scores are stated in the results table below. The 'Critical Appraisal of a Survey' tool was used to appraise all survey studies that have been included in this literature review to ensure that the choice of included studies were of a reasonable quality – Table 4 shows the quality assessment scoring of the survey/questionnaire studies.

2.3 Literature review results

2.3.1 Results of the search and selection procedures

After elimination of duplicates, 1888 unique citations were screened against the eligibility criteria (Figure 3). Following review of title and abstract, 1589 records were excluded. 299 full text articles were obtained and reviewed for inclusion, using eligibility criteria described earlier in this chapter. A final number of 25 full text articles were obtained and used for the purposes of this review of the literature, these comprised 12 studies that used qualitative methods for analysis of data, and 13 studies that used questionnaire/survey data.

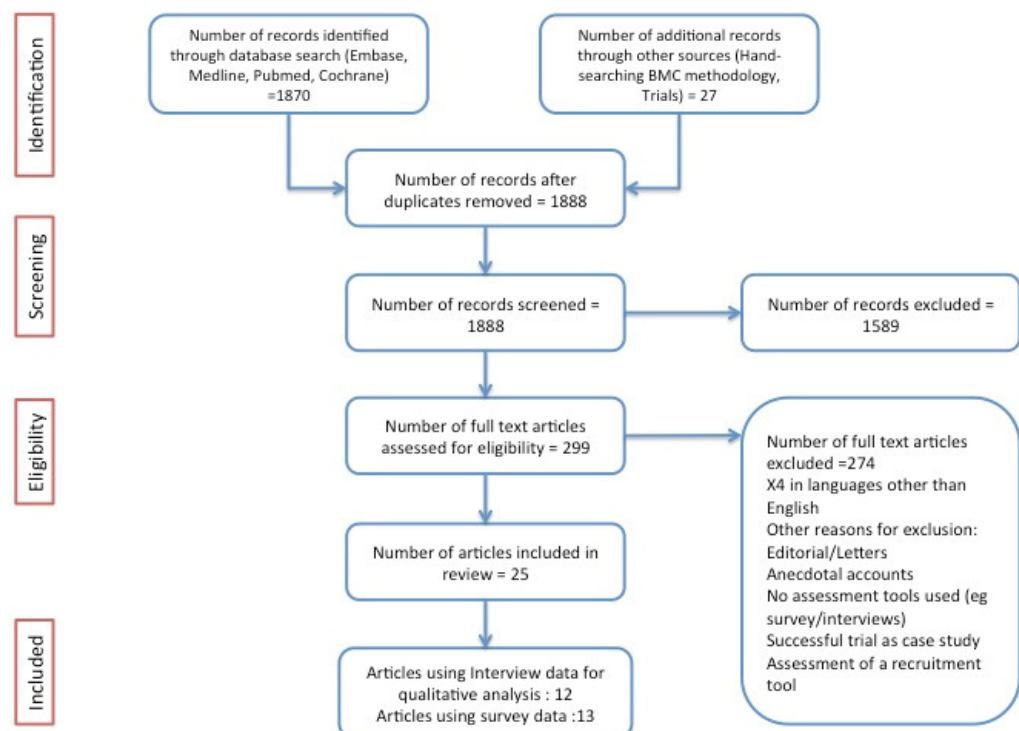


Figure 3. Flow of studies into the review

2.3.2 Description of studies

The following tables describe the studies that were identified – Table 1 describes the 12 studies that have used qualitative methods for analysis. All used interview data, with the exception of one study (Keightley et al (59)) which used free text responses from a survey to examine for themes and draw conclusions. Table 2 shows the quality appraisal of the qualitative studies using the CASP checklist.

Table 3 describes the 13 studies that used survey or questionnaire data to evaluate recruitment issues that were associated with the RCTs. Following this, table 4 is a quality appraisal of these studies.

Of the studies outlined in Table 1, six studies were integrated into an RCT, and took place whilst the trial was ongoing – these included Howard (60), Shilling (61), Donovan (62), Donovan (63), Keightley (59) and Strong (64). The remainder were conducted after the RCT had been closed – either due to insufficient recruitment, or following completion of planned trial recruitment requiring trial extension.

Strong et al (64) examined a feasibility study in surgical oncology that had recruited poorly – as this was a feasibility study, the information from the interview data and qualitative analysis could be used to inform the development of the RCT main trial and specific areas of trial design that could be addressed prior to the launch of the RCT at a later date.

Four of the qualitative studies examined trials that had been closed due to poor rates of recruitment – Hamilton (65), Potter (66), Ziebland (67) and Fairhurst (68). The remainder of the RCTs examined suffered from trial delays. Stuart (69) and Maslin-

Prothero (70) looked into trials that had suffered from recruitment delays, but had not closed – and looked into the reasons for recruitment difficulties through gathering interview data following trial completion.

The majority of the qualitative studies used Thematic Content Analysis and Constant Comparison Techniques in order to process data and complete analysis. These methods were used by Donovan (62), Donovan (63) and Strong (64), with the addition of Grounded Theory to examine for emergent themes in the data. Shilling (61) used Interpretive Analysis, Constant Comparison Techniques and used a Framework for mapping and interpretation of data. Potter (66) used a Thematic Framework Approach in order to analyse data (55).

Of the Survey studies that are outlined in Table 3, the majority surveyed trial staff following trial closure - only three had a design where the survey data was obtained whilst the RCT was ongoing, and were integrated into the trial under examination – these included Goodwin (71), Pike (72) and Lannin (73). The survey study authored by Trussell et al (74) was quite unclear – this is reflected in the quality appraisal of the study, which is demonstrated in Table 4 – unfortunately the article contained insufficient detail regarding the stage in the RCT where information was gathered, the nature of the questions asked, and who was surveyed.

The survey studies that were authored by Goodwin (71), Blanton (75), Lannin (73) and Pike (72), all suffered from delays through poor rates of participant recruitment. The remainder of the studies focused on RCTs that failed to make recruitment targets and were closed because of this.

The reasons why the RCTs examined in all of these studies failed to progress are summarized in the fourth column of Table 1 and Table 3. These points will be discussed in the context of the literature in the Synthesis and Analysis parts of this chapter

Table 1 – Summary of included qualitative studies

Author	Parent Trial	Methods used for evaluation	Key observations	Quality assessment
Fairhurst et al (68)1996 General Practice UK	Aim was to determine the clinical effectiveness of counselling in the management of minor psychiatric morbidity in general practice, and establish the feasibility of implementing such a trial design. Three months after the start of the study no patients had been recruited. Two months later only one patient had been recruited to the study and the trial was therefore discontinued. <i>Issue: Poor recruitment rate – Trial closed</i>	Interview data from one GP from each of the eight practices Retrospective Semi-structured interviews Interviews were analyzed inductively and comparison made between responses to identify the main issues	While accepting there was no proof of the effectiveness of counseling - a number of GPs felt sure that certain patients needed it. Fundamental difficulties concerning general practitioners' attitudes to research and their professional responsibilities found to be key issue <i>Area explored – Equipoise Paternalism</i>	Medium
Maslin-Prothero (70) 2006 Oncology UK	Two UK Department of Health (DOH)-funded research projects examining the factors affecting accrual of women to two breast cancer clinical trials (BASO II and IBIS). Both trials had experienced difficulty in recruiting sufficient numbers of patients. <i>Issue: Poor recruitment rate – did not achieve target</i>	21 interviews at recruitment centres – 7 centres recruiting to BASO II and 14 to IBIS Retrospective Semi-Structured Face to Face interviews Thematic content analysis	The following points were identified: adapting local practice to meet the requirements of the trial, The importance of mechanisms that support trials, these include sufficient staff and clinic time, and the commitment of colleagues and local NHS managers. Evidence suggested that surgeons have the best success rate in obtaining consent. <i>Area explored –Time constraints of research</i>	Medium

		Construction of hierarchy of categories	<i>team, Research Environment</i>	
Ziebland et al (67) 2007 Surgery UK	Multi-centre MRC-funded RCT compared an intensive functional rehabilitation programme (FRP) with spinal fusion surgery for treatment of chronic low back pain. Recruitment was slow and the numbers enrolled smaller than planned. Fifteen UK centres recruited 349 participants, a third of those originally anticipated. <i>Issue: Poor recruitment rate – did not achieve targets. Trial closed</i>	Eleven surgeons from eight centres from the South, Midlands and North were interviewed Purposive sampling Retrospective In depth interviews Thematic content analysis, Constant comparison techniques	Misunderstandings about the entry criteria were an important source of confusion about the applicability of the results. Surgeons perception of the trial aims and methods adversely affects who they recruit; if their views affected what the patients are told; and if they mistakenly view the results are unscientific, unreliable and ultimately irrelevant to their practice. <i>Area explored –Inexperience Gatekeeping patient recruitment/paternalism</i>	High
Potter et al (66) 2009 General Practice UK	The main RCT was designed to promote adherence to treatment for people with type 2 diabetes through telephone support. Participants were randomised to receive telephone support from a Diabetes Specialist Nurse, or a peer supporter, or received routine care only over a 6-month period. The study protocol anticipated recruitment of 375 participants. However, the final number of participants recruited was 231. <i>Issue: Poor recruitment rate – did not achieve targets. Trial closed</i>	10 practice nurses were interviewed Purposive sampling Retrospective Semi-structured telephone interviews A thematic framework approach was used to analyse the data.	Nurses were happy to take part in the trial, except for those nurses delegated the role of recruitment without any form of negotiation who understandably felt put upon. Over 50% of the nurses felt that they would have liked dedicated time to support recruitment. Nurses can act as gatekeepers to recruitment unintentionally causing sample bias and potentially restricting patients' choice to take part in clinical trials <i>Area explored –Time constraints Gatekeeping patient recruitment/paternalism</i>	High

Howard et al (60) 2009 Mental Health UK	The SWAN trial was an RCT of supported employment provided by employment consultants integrated within community mental health teams (CMHTs). Slow recruitment after the first year of the trial. 100 patients had entered the trial (planned total after 1 year was 144). <i>Issue: Poor recruitment rate – did not achieve targets. Delayed</i>	Interviews with four trial staff — Chief Investigator, Principal Investigator, trial coordinator and the research nurse — followed by two Clinical Coordinators Qualitative study integrated in RCT Semi-structured interviews with practitioners Thematic content analysis, Constant comparison techniques	Five main reasons for recruitment difficulties were found. These included: (i) misconceptions about trials, (ii) lack of equipoise, (iii) misunderstanding of the trial arms, (iv) variable interpretations of eligibility criteria, (v) paternalism. <i>Area explored –Equipoise Recruiter inexperience</i>	
Shilling et al (61) 2011 Paediatrics UK	RECRUIT [processes in recruitment to randomised controlled trials of medicines for children] ran alongside four placebo-controlled, double-blind RCTs of medicines for children. All 4 trials examined were struggling with recruitment. <i>Issue: Poor recruitment rate – did not achieve targets. Delayed</i>	31 practitioners from eleven paediatric clinical trials centres that were recruiting to the 4 trials that were under scrutiny. Qualitative study integrated in RCT Semi-structured interviews with practitioners Interpretive analysis, constant comparison method. Themes as categories into a framework for analysis	The concerns of some practitioners that families would be overburdened were unfounded, as parents did not object to being asked about research. Parents and young people often described the trial discussions in strongly positive terms. Informed consent training could be enhanced. <i>Area explored –Paternalism, Consent process (Design)</i>	High
Hamilton et al (65) 2013	Parent Trial: Qualitative research methods were used to explore the feasibility of	Interview data from three surgeons and three recruiters from three	Surgeons and nurses undertaking recruitment were not in equipoise between the two trial arms and didn't fully agree with	High

ENT Oncology UK	launching a large RCT in laryngeal cancer: the EaStER study The EaStER study closed after only recruiting 15 patients. <i>Issue: Poor recruitment rate – Trial closed</i>	feasibility study centres Qualitative study integrated in RCT Semi-structured interviews and focus groups Thematic content analysis, Constant comparison techniques	the trial protocol. Surgeons differed about the factor that should be used as the primary outcome. Recruiters tended to present the secondary outcome as the rationale for the trial to patients. As the recruiters were in equipoise, patients' views, beliefs and preferences were not always carefully elicited or addressed by recruiters. <i>Area explored –Equipoise, Recruiter inexperience</i>	
Keightley et al (59) 2014 Dentistry UK	Parent Trial: Multicentre paediatric primary dental care randomized controlled trial 'Filling children's teeth – indicated or not' (FiCTION) Trial had a lower than anticipated rate of recruitment of participants in the first 12 months. Failed to meet targets and delayed. <i>Issue: Poor recruitment rate – did not achieve targets. Delayed</i>	39 responses to the web-based survey tool. (13 principal dentists, 4 dentists, 12 dental nurses and 10 practice managers) Qualitative study integrated in RCT Data consisted of a survey. Quantitative scores aggregated, and qualitative responses grouped into themes. Thematic content analysis	Main findings: Few practices had ever participated in research before. Practice team did not feel motivated/recognized. The workload for trial administration often fell to one member of the team in the practice. Positive support lacking from central trials team – to help with administration and support recruiting teams. <i>Area explored –Recruiter inexperience, time-constraints</i>	Medium
Donovan et al (63) 2014 Various	The six RCTs included were pilot/feasibility studies, pragmatic in design, funded by national bodies, and encompassed a range of clinical contexts, different types of intervention, and types of recruitment staff.	32 interviews with doctors that were involved in above 6 RCTs – including all CIs. (x21 surgeons x3 GPs x3 community mental health workers, x5 Oncologists)	Main findings: Doctors in this study, including surgeons, wanted to participate in RCTs to gather high-quality evidence. They tried to rely on a sense of community or individual equipoise but experienced	High

UK	All six RCTs suffered from poor recruitment. <i>Issue: Poor recruitment rate – did not achieve targets. Delayed</i>	Qualitative study integrated in RCT Qualitative interview study-Semi-Structured Topic Guide-Face to Face/Telephone Thematic content analysis, Constant comparison and grounded theory	considerable discomfort, intellectually and emotionally, in relation to their clinical and research roles. Difficulty in expressing uncertainty also an issue. <i>Area explored –Equipoise, Consent process</i>	
Donovan et al (62) 2014 Various UK	The research was undertaken in six publicly-funded RCTs in a range of clinical contexts, with different types of RCT intervention, with a range of primary recruiters, and at different stages of the implementation of the RCT. The RCTs were either experiencing severe recruitment problems, or were pilot/feasibility studies expecting difficulties. <i>Issue: Poor recruitment rate – did not achieve targets. Delayed</i>	Interviews with 72 individuals (32 doctors or RCT Chief investigators (CIs); 40 nurses/ other health professionals Qualitative study integrated in RCT Qualitative interview study-Semi-Structured Topic Guide-Face to Face/Telephone) Thematic content analysis, Constant comparison and grounded theory	Disruption of the usual doctor- (or nurse-) patient relationship. Issues regarding recruiter understanding of the principles of RCTs and explanation of the rationale for the RCT to potential participants, issues with confidence in admitting uncertainty, and eliciting patient preferences and provision of accurate information. <i>Area explored –Equipoise</i> <i>Paternalism</i> <i>Recruiter inexperience,</i> <i>Consent process</i>	High
Stuart et al (69) 2015	The multi-site randomised controlled trial aimed to examine if provision of gFNP (Group Family Nurse Partnership), compared to routine	13 community midwives interviewed (17 names supplied to researchers)	Main findings: Trial had low priority (High clinical workload and depleted workforce). Midwifery team had limited knowledge	High

Midwifery UK	antenatal and postnatal services, could reduce risk factors for child maltreatment. Poor recruitment – fell short of the expected 300 (207) Community midwives only identified 18% of these. <i>Issue: Poor recruitment rate – did not achieve targets. Delayed</i>	Retrospective Semi-Structured Face to Face interviews Thematic content analysis	about intervention. Complex eligibility requirements. Concern about the quality of the intervention being offered. <i>Area explored - Equipoise. Recruiter inexperience and time-constraints of research team</i>	
Strong et al (64). 2016 Surgical Oncology UK	Study nested within a feasibility RCT to establish whether a full trial comparing a surgical with a non-surgical intervention for localized squamous cell carcinoma (SCC) was viable. 375 patients discussed across 3 centres. 42 eligible. Only 5 randomised. <i>Issue: Poor recruitment rate - did not achieve targets. Study redesigned</i>	21 interviews (8 surgeons – inc. CI and PI, 5 Oncologists – inc PI, 5 Research nurses, 1 Specialist UGI nurse, 1 research fellow, 1 trials coordinator) Purposive sampling Qualitative study integrated in RCT Qualitative interview study-Semi-Structured Topic Guide-Face to Face/Telephone Thematic analysis – Grounded theory	Main findings: (reasons for poor recruitment rate) Clinician bias towards certain treatments, Poor team functioning. <i>Area explored –Equipoise, Research infrastructure</i>	High

Table 2 – Assessment of quality in qualitative studies (CASP checklist)

Article	Aim	Design Appropriate	Recruitment	Data collection	Relationship Between Researcher and Participants	Ethics Approval	Informed Consent	Data Analysis	Findings
Fairhurst et al (68)1996	✓	✓	Clearly explained	✓	X	X	X	- Analysts not identified - More info needed	Themes not discussed
Maslin-Prothero (70) 2006	✓	✓	Clearly explained	✓	X	X	✓	- Analysts not identified - More info needed	Clearly described. Themes discussed
Ziebland et al (67) 2007	✓	✓	Clearly explained	✓	✓	✓	✓	Clearly described	Clearly described. Themes discussed
Potter et al (66) 2009	✓	✓	Clearly explained	✓	X	✓	✓	Clearly described	Clearly described. Themes discussed
Howard et al (60) 2009	✓	✓	Clearly explained	✓	✓	X	X	Clearly described	Clearly described. Themes discussed

Shilling et al (61) 2011	✓	✓	Clearly explained	✓	✓	✓	✓	Clearly described	Clearly described. Themes discussed
Hamilton et al (65) 2013	✓	✓	Clearly explained	✓	X	✓	✓	Clearly described	Clearly described. Themes discussed
Keightley et al (59) 2014	✓	✓	Clearly explained	✓	X	X	X	Clearly described	Clearly described. Themes discussed
Donovan et al (63) 2014	✓	✓	Clearly explained	✓	X	✓	✓	Clearly described	Clearly described. Themes discussed
Donovan et al (62) 2014	✓	✓	Clearly explained	✓	X	✓	✓	Clearly described	Clearly described. Themes discussed
Stuart et al (69) 2015	✓	✓	Clearly explained	✓	✓	✓	✓	Clearly described	Clearly described. Themes discussed
Strong et al (64). 2016	✓	✓	Clearly explained	✓	X	✓	✓	Clearly described	Clearly described. Themes discussed

✓ = Present in article

X = Not found in article

Table 3 – Summary of included Survey/Questionnaire studies

Author	Parent Trial	Methods for evaluation	Key Findings
Goodwin et al (71) 2000 Oncology Canada	The BEST Study was a multicenter, randomized trial comparing usual care with alternative forms of psychosocial support for patients with breast cancer. Recruitment took approximately 50% longer than expected and required the involvement of two additional centers. <i>Issue: Poor recruitment rate – did not achieve targets. Delayed</i>	Seventeen active leaders (recruiters) responded to the survey Response rate, 100% Retrospective Questionnaire	Competing clinical trials were the greatest barrier to recruitment. Also, no established, systematic approach to identification and recruitment of patients, and the unwillingness of a significant proportion of potentially eligible patients to participate in the study. <i>Area explored- Time-constraints of research team, Research infrastructure, Trial design – available patients/unacceptable intervention</i>
De Wit et al (76) 2001 General Practice The Netherlands	Primary care study of dyspepsia, the CIRANO study (Cisapride or Ranitidine in NonOrganic dyspepsia), which was conducted from 1996-1998 in the Netherlands. A total of 165 Family Practitioners (FPs) signed the research contract. 21% of the FPs did not recruit any patients. Recruitment fell short of predictions <i>Issue: Poor recruitment rate – Trial closed</i>	Questionnaire data from 128 FPs used for analysis Response rate was 80% Retrospective Questionnaire	Successful participation is mainly determined by the initial motivation of the FP: Those with a strong affiliation with academic research unit and resources, and previous experience recruit best. The research topic, the amount of the financial incentive, and other factors often suggested to influence patient recruitment are probably less important. <i>Area explored – Research infrastructure, Recruiter inexperience</i>

Blanton et al (75) 2006 Physical Therapy USA	The recruitment process for the Extremity Constraint- Induced Therapy Evaluation (EXCITE) trial illustrates obstacles to and strategies for participant accrual and retention that are inherent in rehabilitation clinical trials. The process of recruitment took 13 months longer than expected. <i>Issue: Poor recruitment rate – Trial delayed</i>	Questionnaire data from 6 study site project coordinators. Response rate 100% Retrospective Questionnaire – closed and open ended questions	A frequent temptation during recruitment was to describe EXCITE trial participation as an additional opportunity for extra therapy. Participants did not always have a clear understanding of potential benefits and risks, or a list of who to contact if they have concerns or questions. Stringent inclusion and exclusion criteria affected the rate of patient accrual <i>Area explored – Study design – inclusion/exclusion criteria, Recruiter inexperience</i>
Lannin et al (73) 2006 Occupational Therapy Australia	Trial investigated the effect of adding contracture management hand splinting to rehabilitation following stroke. Eligible patients were from six consenting acute rehabilitation hospitals. It was intended that 63 patients would be recruited over 18 months. After 18 months only 50 had been enrolled. <i>Issue: Poor recruitment rate – did not achieve targets. Delayed</i>	Questionnaire data from 18 occupational therapists Response rate of 78% Study integrated into RCT Questionnaire – closed and open ended questions	Therapists who have attained research qualifications (or are getting them) are more effective recruiting patients for a randomized controlled trial than other therapists. Choosing not to refer patients because of concern for their medical prognosis was the only patient-related factor that was significantly related to recruitment rate. <i>Area explored – Recruiter inexperience, Gatekeeping patient recruitment/paternalism</i>
Spaar et al (77) 2009 Medicine Switzerland	The trial was a multi-centre RCT on respiratory rehabilitation in COPD patients in Switzerland. From September 2006 to January 2009, only 37 patients were randomized, the target sample size	Questionnaire data from 38 recruiting physicians. Response rate 69%	Recruiting physicians reported that "time constraints" had the most negative impact on recruitment followed by "difficulties including identified eligible patients". Other barriers such as "trial design barriers", "lack of access to treatment", "individual barriers of recruiting

	was 280. <i>Issue: Poor recruitment rate – Trial closed</i>	Restrospective Questionnaire	physicians" or "insufficient training of recruiting physicians" were perceived to have little or no impact on patient recruitment. <i>Area explored- Study Design – inclusion/exclusion criteria, Time-constraints of research team</i>
Page et al (78) 2011 General Practice Australia	The IMPLEMENT CRT was publically funded to test the effectiveness of a theory-based intervention guideline for acute non-specific low-back pain into general practice. The authors aimed to recruit 2300 patient participants from 92 practices. However, after 9 months of recruitment, only 287 patients had been invited during that period – 28% of GP practices had not invited any patients. <i>Issue: Poor recruitment rate – Trial closed</i>	Questionnaire data from 79 GPs Response rate 84% Retrospective Questionnaire – closed and open ended questions	While GPs intended to recruit patients, barriers such as time constraints and forgetting to recruit patients may have contributed to poor recruitment. Trialists need to develop and evaluate patient recruitment strategies that minimise the efforts required by practice staff to recruit patients. <i>Area explored– Study design – inclusion/exclusion criteria Recruiter inexperience, Time constraints</i>
Lægreid et al (79) 2011 Nephrology Norway	Multicentre RCT targeting end-stage renal disease (ESRD) patients older than 70 years was initiated to compare the impact on quality of life of early or late start of dialysis. The plan was to include 110 patients in each group, 220 altogether. After 16 months only six patients had been included and the trial closed. <i>Issue: Poor recruitment rate – Trial closed</i>	Questionnaire data from 39 Norwegian Nephrologists Response rate 36% Restrospective Questionnaire	The highest rated reasons for non-inclusion were the physician's wish to decide the timing of dialysis individually. High mean scores were also found for reasons related to workload and capacity at the dialysis unit, whereas the influence of the doctor-patient relationship and competing studies were judged not to be important. <i>Area explored – Time constraints, Gatekeeping patient recruitment/paternalism</i>

Trussell et al (74) 2011 Urology USA	Trial entitled “A Prospective, Randomized Study of Microsurgical Varicocelectomy versus No Surgery in the Treatment of Male Partners with a Palpable Varicocele and an Abnormal Semen Analysis” This study screened 7 and enrolled 3 couples in the first year. The study was subsequently closed. <i>Issue: Poor recruitment rate – Trial closed</i>	Questionnaire data from 3 urologists, 5 reproductive endocrinologists, and a reproductive geneticist. (9 participants) Response rate – not reported Retrospective Questionnaire	Barriers to recruitment included: Patient intolerance of a placebo arm, and bias against one of the interventions (preference for surgical intervention). Investigators suggested focused patient education may promote improved ‘equipoise’ and acceptance of a placebo arm, also having a network of researchers who carry a high volume of possible study participants, as screening of very large numbers may be needed to complete clinical trial enrollment. <i>Area explored – Study design –inclusion/exclusion criteria, Recruiter inexperience, Equipoise</i>
Geynisman et al (80) 2012 Oncology USA	A multicenter, randomized, double-blind, placebo-controlled, phase 2 study to test the hypothesis that androgen replacement in men with low-risk metastatic CRPC (castration resistant prostate cancer) can inhibit cancer growth. 60 pts per arm anticipated. Trial recruited 11 pts over 2yrs from 12 sites, and closed due to poor recruitment. <i>Issue: Poor recruitment rate – Trial closed</i>	Questionnaire data from 15 recruiting oncologists Response rate 88% Retrospective Questionnaire	Specific reasons for patient refusal to participate were (1) lack of comfort with using testosterone (57%), (2) lack of comfort being randomized to placebo (57%), (3) difficulty understanding trial rationale (29%), (4) desire for other treatments (43%), and (5) trial requirements too difficult (21%). Ten oncologists (67%) noted that strict eligibility criteria were a major hindrance for them to offer the trial to more patients <i>Area explored – Study design- inclusion/exclusion criteria, Equipoise</i>
Costescu et al (81) 2013	The parent trial was a small randomised clinical trial to compare two methods of induction of	Questionnaire data from 8 obstetricians and 13	Overestimation in the number of patients available for inclusion in the study, no financial incentive for

Obstetrics Canada	labour in women. Standard therapy versus standard therapy plus intervention. 40 patients per arm anticipated. Over first 2 years only 5 randomised. <i>Issue: Poor recruitment rate – Trial closed</i>	residents Response rate, Obstetricians 67%, Residents 93%. Retrospective Internet-based questionnaire	clinician time/participant involvement. No involvement of study nurse. Busy staff with clinical commitments. Patients found the intervention unacceptable. <i>Area explored – Trial design/Availability of eligible patients/Intervention unacceptable, research infrastructure, Recruiter inexperience, time-constraints</i>
Pike et al (72)2013 Paediatrics USA	This double-blind, randomised placebo-controlled trial compared the effects of enalapril with placebo on somatic growth in 230 neonates with functionally univentricular hearts. After the first 6 months, recruitment was only 28% of the target rate across the seven sites, this led to an extension of recruitment period, leading to cost implications for the trials team. <i>Issue: Poor recruitment rate - Delays</i>	Questionnaire data from 10 recruitment centres Response rate 100% Study integrated into RCT Questionnaire	The following characteristics of centres aided in recruitment: a strong infrastructure for research; support from clinical staff; and a programme in foetal cardiology. <i>Area explored – Recruiter inexperience, Research infrastructure</i>
Ferris et al (82) 2013 Nephrology USA	The focal segmental glomerulosclerosis clinical trial (FSGS CT) was a publically funded, multicenter, open-label, randomized comparison of cyclosporine versus oral dexamethasone pulses plus mycophenolate mofetil. Enrollment was slow from the onset of the study and, therefore the enrollment period was extended	Questionnaire data from 47 recruiting sites Response rate 45% Retrospective	Barriers to patient recruitment : Specific eligibility criteria, Low prevalence of disease at site, concern about choice of drugs and doses being used, reluctance of nephrologists to relinquish their determination of individual patient treatment. There were logistical issues such as the time required to obtain IRB approval

	from 26 to 40 months. It fell far short of its anticipated goal of 500 participants. <i>Issue: Poor recruitment rate – Trial closed</i>	Web based anonymous questionnaire	<i>Area explored –Study design- inclusion/exclusion criteria, Recruiter inexperience, Research infrastructure - Permissions from regulatory authorities, Paternalism.</i>
Foster et al (83) 2015 General Practice UK	In a primary care-based professional-cluster RCT of interventions to improve adherence and disease control in adults with asthma (the Management to Improve Control of Asthma or ‘MICA’ study) Planned for recruitment of 220 patients from 44 practices. Recruitment of 44 GPs delayed. After 6 months, they had recruited 119 of the planned 220 patients. At completion of patient recruitment, 143 patients had been enrolled. 15/55 (27%) GPs did not enroll any patients. <i>Issue: Poor recruitment rate – Trial closed</i>	Questionnaire data from 42 GPs (37 recruited patients) Response rate 76% Retrospective Questionnaire – closed and open ended questions	Recruitment barriers at the level of GP (e.g. GPs excluding patients for whom research appeared too challenging), practice (e.g. practice cultures disempowered GPs), patient (e.g. reluctance to change treatment for research) and study (e.g. protocol requirements complicating recruitment). Facilitators included GPs perceiving good support from the research team. <i>Area explored – Trial design – Unacceptable intervention/Inclusion-exclusion criteria, Recruiter inexperience, Research infrastructure</i>

Article	Clear question	Design Appropriate	Selection of subjects described	Risk of selection bias?	Sample of subjects representative of population?	Statistical significance of sample size considered?	Response rate satisfactory?	Measurements (questionnaires) likely to be valid/reliable?	Statistical significance assessed?	Confidence intervals given?	Confounding factors?	Results applicable to organization?
Goodwin et al (71) 2000	✓	✓	✓	X	✓	X	✓ (100%)	✓	X	X	✓	✓
De Wit et al (76) 2001	✓	✓	✓	X	✓	X	✓ (80%)	✓	✓	✓	X	✓
Blanton et al (75) 2006	✓	? (Unclear)	✓	X	✓	X	✓ (100%)	? (Unclear)	X	X	✓	✓
Lannin et al (73) 2006	✓	✓	✓	X	✓	X	✓ (78%)	✓	✓	X	X	✓
Spaar et al (77) 2009	✓	✓	✓	X	✓	X	✓ (69%)	✓	X	X	X	✓
Page et al (78) 2011	✓	✓	✓	X	✓	X	✓ (84%)	✓	✓	✓	X	✓
Lægreid et al (79) 2011	✓	✓	✓	X	✓	X	X (36%)	✓	X	X	X	✓
Trussell et al (74) 2011	X	? (Little detail)	X	? (Unclear)	✓	X	? (No details)	? (No details)	X	X	? (No details)	✓
Geynisman et al (80) 2012	✓	✓	✓	X	✓	X	✓ (88%)	✓	X	X	X	✓

Costescu et al (81) 2013	✓	✓	✓	X	✓	X	✓ (67% and 93%)	✓	X	X	X	✓
Pike et al (72) 2013	✓	✓	✓	X	✓	X	✓ (100%)	? (No details)	X	X	X	✓
Ferris et al (82) 2013	✓	✓	✓	X	✓	X	X (45%)	✓	✓	✓	X	✓
Foster et al (83) 2015	✓	✓	✓	X	✓	X	✓ (76%)	✓	✓	✓	X	✓

Table 4 – Critical Appraisal of Survey Studies

✓ = Present in article
X = Not found in article
? = Unclear

2.3.3 Synthesis

In this section, I will first describe key concepts suggested by studies that have looked at groups of trials (Trials in certain healthcare sectors or funded by certain bodies) and have explored factors that have influenced recruitment and have characterized these factors that are likely to affect recruitment. Second, I will look at previous reviews of the literature that report difficulties in recruiting to RCTs. I will use this information to inform my choice of themes by which to look at the articles that were found as a result of my literature searches and described in tables 1 and 3.

2.3.2.1 Studies of groups of RCTs examining difficulties in recruitment

There are a number of published studies that have examined recruitment issues in RCTs. The studies that have been outlined below have looked at series of trials – funded by particular funding body, or in a particular sector (General Practice in the case of Bower et al (84)) and examined the trends in recruitment – and if there are factors that may have been common to those trials that have been less successful in recruiting patients to planned targets.

The reasons for poor recruitment to RCTs can be found at various levels, that of the trial design and planning, at the level of the clinician and trial subject's readiness to participate in the trial, and the infrastructure within which the trial takes place (85).

Author	Title	Country/Year	Key Findings
Charlson et al (86)	Applying results of randomized controlled trials to clinical practice: Impact of losses before randomisation	USA/1984	A survey of 41 trials conducted in North America – listed in the inventory of the National Institute of Health. Authors found that 66% of trials never achieved their projected sample size. The largest losses before randomisation occurred as a result of the study criteria and not as a result of the refusal of patients or their physicians to participate. Half of the losses of eligible patients occurred because of the application of restrictive eligibility criteria.
Easterbrook et al (24)	Fate of research studies	UK/1992	A retrospective survey of 720 research protocols submitted to the Central Oxford Research Ethics Committee (COREC) between 1 January 1984 and 31 December 1987. Of the 487 studies for which information on current status was obtained, approximately one-third either never started or were subsequently abandoned. The main reason cited for abandoning a study was that there were an insufficient number of study participants. In many cases, the small sample size was attributable to a failure to enroll sufficient patients, rather than to an absence of prior planning for an adequate number of patients – suggesting restrictive eligibility criteria.
McDonald et al (21)	What influences recruitment to randomized controlled trials? A review of trials funded by two UK funding agencies	UK/2006	114 trials identified from databases held by two UK funding bodies – with recruitment from 1994-2002. 38 (31%) trials were assessed to have recruited ‘successfully’ (i.e. 100% of their original target). A further 29 (24%) of trials achieved a recruitment rate of at least 80% but less than 100% of their original target. Thirteen trials recruited to their original target after a time extension. The start of recruitment was delayed in 47 (41%) of trials. Main reasons cited were: delays related to central trial staff (11 trials); local research staff (11 trials); and local clinical arrangements (7 trials). The most commonly reported problem with early recruitment was that fewer than expected eligible patients were being observed (19 trials).
Bower et al (84)	Short report: how often do UK primary care	UK/2007	Survey of 39 primary care trials in the UK. Only 29% of trials recruited to timetable, with 70% of cases requiring extra time.

	trials face recruitment delays?		If GPs were responsible for gaining patient consent, only 12.5% of trials recruited within 50% of the planned time, compared with 61.5%, where the GP was not responsible.
Sully et al (20)	A reinvestigation of recruitment to randomised, controlled, multicenter trials: a review of trials funded by two UK funding agencies	UK/2013	Review of 73 trials funded by the HTA and the UK MRC between 2002 and 2008. Methods replicated from McDonald et al (21). The recruitment target was only met in 40 (55%) of trials; meanwhile, 17 (23%) trials recruited to 80% but less than 100% of their target. The impact of clinical trials units (CTUs) on trials is positive. A total of 31 (42%) trials had CTUs involved, down from 78% in 1994 to 2002. Of these 31, 20 (65%) recruited successfully, while trials without CTUs successfully recruited only 48% of the time (19 trials).

Table 5 – Studies of group of RCTs – examining the difficulties in recruitment

In Table 5, the studies illustrated identify a number of areas that were identified as particular areas of concern, and responsible for the poor recruitment rate in each series. Charlson 1984 (86), Easterbrook 1992 (24) and McDonald 2006 (21) all report issues with ‘fewer than expected eligible patients’. This phenomenon, known as ‘Lasagna’s law’ states that medical investigators tend to overestimate the number of patients that meet the inclusion criteria for a research study (87) (88) and can reflect a complex, or restrictive inclusion and exclusion criteria (89), and is therefore an aspect of trial design.

McDonald 2006 (21) and Sully 2013 (20) report issues with staff availability, and involvement of CTUs respectively. These all relate to the infrastructure – or research environment where the trial is taking place. These issues can affect patient recruitment – in particular as working within a ‘Research Ready’ setting can potentially avoid delays in trial set-up, such as obtaining approvals and securing NHS costs (90). Bower reports that involvement of GPs (which the paper explains, are largely research naïve in the population surveyed) in consenting patients, rather than core research staff was associated with poor recruitment. Clinicians’ understanding of research in general and RCTs in particular has been reported as a barrier to patient recruitment (25).

2.3.2.2 Review articles – the difficulties with recruiting to RCTs

The table below summarises 5 review articles that examine the literature around the areas of successful recruitment to clinical trials, and more specifically those factors that pose challenges to meeting recruitment goals within a specified timeframe and budget.

Author/Type of study	Aim of study	Areas explored in review	Findings
Hunninghake et al 1987 (91) Literature summary and annotated bibliography 1966-1986 85 papers included	A literature review conducted to determine what problems exist in accruing adequate numbers of patients for clinical trials.	Recruitment outcomes Planning Management Participant and physician characteristics and attitude	A strong administrative component is needed at both central and local levels Physicians would be more favourably disposed to the involvement of their patients if they believe the research is important, and equal chance of success in all treatments Lack of experience in trials a major cause of recruitment failure
Lovato et al 1997 (92) Literature summary and annotated bibliography 1986-1995 91 papers included	A literature review of recruitment strategies in clinical trials; explore recruitment strategies that may be helpful to individual studies; and highlight areas where documentation of recruitment experience is needed.	Diverse populations Recruitment strategies Planning and management Participant and physician attitudes	Specific recruitment strategies should be used for inclusion of ethnic minorities/women etc Role of trials coordinator important The most commonly identified barriers to physicians' enrolling patients are excessive time commitment for either physician or participant, intrusion on the patient/physician relationship, the obtaining of informed consent, imposed financial burden, and disagreements with trial protocol design
Prescott et al 1999 (17) Database searches 1986-1996 270 papers included. 2 qualitative studies	Systematic review of the literature to assess factors which might limit the quality, number, and progress of NHS controlled trials	Design issues Barriers to participation in trials Factors relating to the conduct and structure of RCTs	Pilot studies recommended to assist trial design Clinically relevant outcome measures/Simple, clear entry criteria/demands of the study to be kept minimal. Inexperienced trialists should be supported by those more experienced/trials benefit from a steering group and trials coordinator
Ross et al 1999 (93) Database searches 1986-	Systematic literature review of barriers to clinician and patient participation in	Clinician barriers Participant barriers	The trial should address an important research question The protocol and data collection should be as straightforward as possible.

1996 78 papers included	randomised trials		The demands on clinicians and patients should be kept to a minimum. Dedicated research staff may be required to support clinical staff and patients
Toohar et al 2007 (94) Database searches 1966-2006 53 studies included. 11 qualitative studies	A review of the literature regarding recruitment to maternal and perinatal trials in order to identify barriers and enablers to successful recruitment	Participant factors which influence recruitment Clinician factors which influence recruitment Strategies to enhance recruitment to randomised trials	Support from a clinical trial coordinator or research nurse with responsibility for trial recruitment was found to be positively linked to recruitment in two studies In designing trial protocols, investigators could aim to use simpler rather than more complex designs When possible, the trial design could use standard care as the basic treatment model

Table 6 Reviews of the literature – difficulties in recruitment to RCTs

From consideration of issues highlighted in the groups of studies outlined in tables 5 and 6, it is possible to summarise the broad areas which present a risk to the fulfillment of recruitment targets. I have separated these areas into three overarching areas – or themes, and will use this as the basis of the analysis of the studies described in Table 1 and 3.

- Study Design
 - Planning
 - Including, inclusion and exclusion criteria, patient availability
- Clinician and Participant Factors
 - Including, equipoise, time constraints and paternalism
- The Research Environment
 - Management
 - Including, research infrastructure and previous experience of research

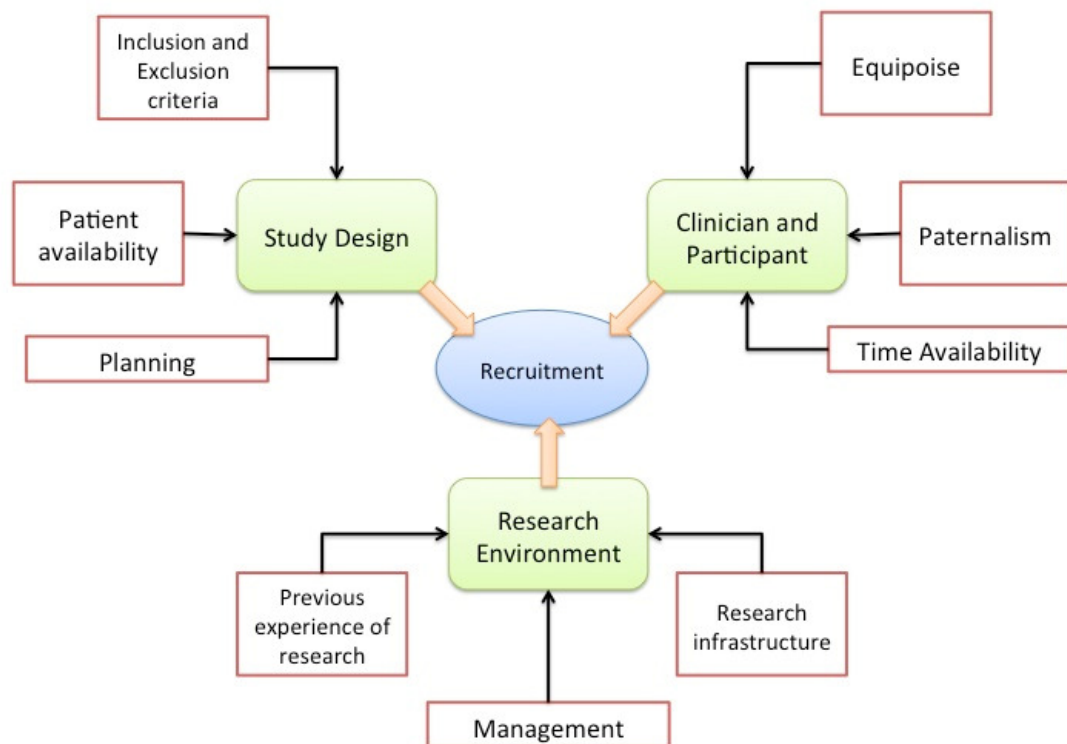


Figure 4. Themes that contribute to participant recruitment

2.3.4 Key Findings – What prevented participant recruitment?

2.3.3.1 Overview

A number of key areas that represent barriers to participant recruitment are illustrated in the table below. A number of factors have been identified through this review of the literature, in particular those areas associated with the research environment.

Study references – relating to the qualitative studies and the survey studies found as part of the literature searches – are listed in the third column.

Table 7 Thematic analysis

Second Order	First Order	References
Study Design	Inclusion/Exclusion criteria	(74, 75, 77, 78, 80, 82, 83)
	Consent process	(61-63)
	Available patients	(71, 81)
	Acceptability of intervention	(71, 81, 83)
Clinician and Participant Factors	Equipoise	(60-65, 68, 69, 73, 74, 80)
	Paternalism	(60, 62, 66-68, 73, 79, 82)
	Gatekeeping patient recruitment	(66, 67, 79)
The Research Environment	Research Infrastructure	(64, 70-72, 76, 81-83)
	Recruiter Inexperience	(59, 60, 62, 65, 67, 69, 72-76, 78, 81-83)
	Time constraints	(59, 66, 69-71, 77-79, 81)

2.3.3.2 Theme: Study Design

Study design is an important starting point for any trial, and requires thorough consideration in order to maximize chances of success. Feasibility and pilot studies are encouraged by funding organisations, and are seen as a way of taking reasonable precautions, and to be able to re-visit study protocol, change strategy and reduce the risk of a trial falling short of expected targets.

In the study by McDonald et al (21) – out of 114 trials examined, sixty (53%) had conducted a formal pilot study – of these 32 indicated that the pilot study had led to change in recruitment strategy. Only one of the studies examined from the literature, that by Strong et al (64), was nested in a pilot/feasibility study – potentially giving

the researchers involved in the development of the full RCT the ability to address all possible factors – including radical overhaul of inclusion/exclusion criteria, the intervention being assessed, and the patient population to be examined. The remainder of the studies – both qualitative and survey studies – involved assessment of trials that had been funded based on the trial design and establishment of specific protocols, and were either ongoing, or had already closed. This is reflected in the spread of studies that were identified as having issues in the areas ‘Inclusion/Exclusion Criteria’ – these were all studies that had closed at an early stage due to poor recruitment, and the timing of the surveys/interviews was after the trial had closed completely.

Choosing a patient population to test a particular intervention is an important consideration. Complicated and restrictive inclusion and exclusion criteria mean that the potential population for recruitment will become lower, and this also has an impact on the number of potential ‘available patients’. When investigating a rare disease condition, or working in a small organization such as a primary care facility where there is a smaller catchment area and therefore a smaller pool of patients can all have an impact on how likely it is to recruit adequate numbers of participants quickly. In the study by Goodwin et al (71) it was found that certain centres struggled more than others to recruit adequate numbers of participants, describing a lack of available patients. The investigators found that by changing the recruiting centres to those that had a different catchment and available pool of patients, that some of these issues could be addressed.

The intervention also has to be reasonable. In the study by Cortescu et al (81) – part of the reason it was so difficult to recruit patients was that standard care was being compared to an intervention that was more time-consuming and uncomfortable for patients. Most participants and clinicians found the intervention unacceptable, and so there were very few study participants put forward for the trial.

2.3.3.3 Theme: Clinician and Participant Factors

The qualitative study by Strong et al (64) was embedded in a feasibility study, and the findings were used to inform changes in the RCT in order to improve recruitment on commencement of the trial – this included factors relating to equipoise, and also ensuring adequate infrastructure for research. In a similar manner, a number of studies that have been found in the literature were embedded in an RCT – whilst recruitment continued, data was obtained with regards to what issues were being faced by recruiting staff, changes could then be put in place in order to avoid trial failure. The qualitative studies that were designed to fulfill this purpose included Howard (60), Shilling (61), Donovan (62), Donovan (63) and Keightley (59). There were a smaller group of survey studies that were designed to fulfill the same purpose, and these were those by Goodwin (71), Pike (72) and Lannin (73).

When it comes to the identification of factors in this group of embedded studies, there is representation of a variety of themes throughout. An important factor that was found in all of the embedded qualitative interview studies (Keightley (59) did not use interview data for analysis) was that of ‘Equipoise’.

Bradford Hill (95) established the principle that a doctor should only include a patient in an RCT if it is that it must be possible ethically to give every patient admitted to a trial any of the treatments involved – that the doctor has no knowledge

that one treatment will be better or worse, safer or more dangerous than another. This view that all treatment options are of equal merit is known as 'Equipoise'. It is conflicts and discomforts around issues of equipoise that can adversely affect participant recruitment – in particular if the researcher, or member of medical staff responsible for identifying potential participants feels that a particular treatment is more suitable for a particular patient. Equally, participants can often have certain beliefs with regards to certain treatments and interventions, and also have a preference for a particular one. Donovan et al (63) suggest training and support for staff that are involved in recruitment – or the use of research staff that are able to present a trial more neutrally to a potential trial participant may help to address equipoise, and promote recruitment.

Paternalism, and a conflict in roles, is related to issues with equipoise, as demonstrated in Howard et al (60) – the behaviour demonstrates the conflict between being a researcher recruiting for a trial and a health professional protecting the interests of patients. Many of the individuals interviewed as part of this study primarily thought of themselves in the caring role for their patients, focusing more on their perception of patient needs than providing patients with the opportunity to decide whether they would like to participate in the research.

As gatekeepers, clinicians may seek to protect people for whom they provide care from the perceived burden of research participation or an intervention perceived to be futile (96). In the study by Laegried et al (79) – the biggest obstacle that the researchers encountered was that the physicians (nephrologists) wished to decide and time the intervention (in this case, dialysis for end-stage renal disease) on an

individual basis with the patient, rather than risk the patient being in either the ‘early start’ dialysis group, or the ‘late start’ dialysis group.

2.3.3.4 Theme: The Research Environment

The study by Ferris et al (82) that looked into issues with recruitment of participants into an RCT looking at an intervention for kidney disease noted significant issues with time delays associated with granting study permissions (IRB approval), long delays between IRB approvals being granted and then the inclusion of the first participants at study sites, and coordination of core clinical infrastructure. These issues causing problems with recruitment is not unusual, and has been noted in a number of articles from the UK as well (97-99)

This can potentially be addressed through trials teams having additional help and support through ‘Clinical Trials Units’ (100) These are multidisciplinary specialist units that have the remit to design, monitor and conduct clinical trials (101). In an environment where regulatory bureaucracy is complicated, and running a clinical trial is more complex, having this support and ‘Research Ready’ infrastructure becomes increasingly essential. Increasingly funders of clinical trials are stipulating the need for RCTs to have an association with CTUs in order to ensure adequate support and availability of expertise (102)

2.3.4 Key findings – Methods used

The studies that have been examined as part of this literature review have, in the most part, looked at one particular trial, or case study. The methods used by the researchers has varied – a proportion used survey methods, and the rest undertook

interviews – the table below illustrates the range of methods used by researchers to obtain and analyse interview data.

Table 8 Methods used to obtain and analyse interview data

Article	Sampling	Data Collection	Analysis Methods
Fairhurst et al (68)1996	Purposive sampling Retrospective	Semi-Structured Interviews	Inductive approach Constant comparison techniques
Maslin-Prothero (70) 2006	Purposive sampling Retrospective	Semi-Structured Interviews	Thematic content analysis
Ziebland et al (67) 2007	Purposive sampling Retrospective	In depth Interviews	Thematic content analysis Constant comparison techniques
Potter et al (66) 2009	Purposive sampling Retrospective	Semi-structured interviews	Thematic framework approach
Howard et al (60) 2009	Purposive sampling Qualitative study integrated in RCT	Semi-structured interviews	Thematic content analysis Constant comparison techniques
Shilling et al (61) 2011	Purposive sampling Qualitative study integrated in RCT	Semi-structured interviews	Interpretive analysis, Constant comparison technique, Framework approach
Hamilton et al (65) 2013	Purposive sampling Qualitative study integrated in RCT	Semi-structured interviews and focus groups	Thematic content analysis Constant comparison techniques
Donovan et al (63) 2014	Purposive sampling Qualitative study integrated in RCT	Semi-structured interviews	Thematic content analysis Constant comparison and grounded theory techniques
Donovan et al (62) 2014	Purposive sampling Qualitative study integrated in RCT	Semi-structured interviews	Thematic content analysis Constant comparison and grounded theory techniques
Stuart et al (69) 2015	Purposive sampling Retrospective	Semi-structured interviews	Thematic content analysis
Strong et al (64). 2016	Purposive sampling Qualitative study integrated in RCT	Semi-structured interviews	Thematic content analysis, grounded theory

In part, the information gained from this literature review will serve in part to validate and contrast the methods that have been used in this thesis. Like a number of the interview studies described above, the research question was formulated after the case study trial had already closed down, therefore, the interviews were conducted retrospectively. Sampling was performed purposively, and interviews were semi-structured. During the piloting phase and initial analysis of the data, interviews were analysed inductively, using grounded theory and examined for emergent themes. Framework was then used. There are examples of all of these techniques being used in the studies described in the table above. However, the results obtained when I made my initial attempt at data analysis did not give me the answers that I had hoped for, although working through the data in this way made me very familiar with the events that had occurred, using a deductive approach with pre-determined framework in order to analyse the data to give the final results described in the Results Chapter was a departure from the way that researchers have looked at similar case studies in the literature.

2.4 Discussion

2.4.1 Literature review summary of findings

This literature review has endeavoured to establish a number of barriers to participant recruitment. Focus has been on trials that have failed to recruit or progress as hoped, and have been terminated due to poor recruitment. The inclusion of majority qualitative studies has made this different to other review articles in the literature that have looked at similar questions.

There is a whole body of literature that has focused on ‘Methods to Improve Recruitment’ to trials (103-105). This looks specifically at interventions that aim to increase participation in clinical trials, and endeavours to inform trialists on how best to design and plan trials such that they are more likely to be successful (25). The areas that are focused on include ‘Trial Design’, ‘Consent’, ‘Approach to participants’, ‘Financial incentives’, ‘Trial administration/Co-ordination’, ‘Training for recruiters’(103). These areas are important, and some of these factors have been highlighted in this review of the literature – However, ‘Research Infrastructure’ does not.

The infrastructure required to conduct a trial is extremely important. Funders can have expectations regarding effective delivery of a trial once it has been funded, and these often complex projects have to be delivered in a timely way, and within budget (106). Clinical trials are not only research activities- the need to deliver an expert result means that they effectively have two interdependent sets of processes – one clinical and the other managerial (107).

Clinical trials units (CTUs) are specialized research units that can help to design and co-ordinate clinical trials, and consist of a ‘research team’ that are knowledgeable and experienced in interacting with key stakeholders (100). They provide a ‘Research Infrastructure’ and are familiar with processes – such as negotiating bureaucracy and permissions to run a clinical trial, such that there is a greater likelihood for a successful outcome, but often the involvement of a CTU can greatly increase the costs associated with running a trial (101). An example of a common

bureaucratic challenge is that of ‘excess treatment costs’ Local NHS organisations are responsible for recovering the NHS treatment costs associated with research, and applying for these can be a lengthy, complicated and unpredictable process – often resulting in long delays, and even trial closure (97, 108) – a problem that research teams with less experience, in an environment that is not ‘Research Ready’ and without the resources to be able to flexibly give the hours of extra management or research staff time to a project, are much more likely to suffer from acutely (108).

Recruiter experience is also an extremely important factor in determining the likelihood of trial success. An important factor – especially with multicenter trials – is to consider the careful selection of trial sites in order to improve chances of recruitment to target – and a centre and team that are ‘Research Ready’ – both in experience and resources available – are more likely to recruit successfully (109). This is particularly noticeable in primary care (general practice) where the experience, and links to resources are likely to be less apparent (90). Although ‘Recruiter Training’ is highlighted in studies that have looked to improve participant recruitment (103), this may not address the full extent of the issues that pose barriers to successful recruitment to clinical trials.

The trials examined as part of this literature review are relevant to this thesis, as the case study trial for examination was a publically funded, multicentre RCT comparing two treatments in a chronic disease condition – like the trials examined in this review, it suffered from delays to recruitment, and was closed due to failures in achieving its planned targets. Through this thesis, the events, documents and accounts from staff that were involved in the trial will be examined, and form the

qualitative study. Like the trials examined above, the interview data will be obtained retrospectively, through semi-structured face-to-face and telephone interviews.

Analysis will involve searching for themes, and using a framework method of analysis (55)

2.4.2 Limitations of review

This literature review was written after the interview data and majority of the data analysis that forms the rest of this thesis had taken place – this may have influenced the themes elicited from the data, and the important points that were gleaned from the literature review. A review of the methods that other researchers have used in similar studies was important in order to validate the methods that were used in this thesis – using ‘The Framework Method’ isn’t common, but has been used in one of the qualitative studies examined (66).

The range of studies examined has included trials that have taken place across a number of speciality areas, across a number of countries. The themes that have arisen through examination of all of these titles have been consistent, despite the nature of the RCT under examination, or the country in which it has taken place – however, a more targeted review appropriate to adult medicine, for example, or paediatric surgery recruitment would be possible as this area of trials research grows.

2.5 Conclusions

In this literature review, methods for examining RCTs in order to assess for reasons for failure or delays in recruitment have been examined – and these have helped to

validate the methods that are used as part of the assessment of the case study trial that is examined in this thesis. Barriers to recruitment have been examined through assessment of the qualitative and survey studies, and supported by the findings of previous large scale survey studies and previous similar literature reviews.

One of the key points that has emerged from this search, has been the importance of 'Recruiter Experience' and having a 'Research Infrastructure' in place (consisting of staff, management support, and may take the form of a 'Clinical Trials Unit') in order to make informed site selection (110), negotiate trial bureaucracy and complicated permissions (111), and to avoid unnecessary delays (98). In an environment that increasingly depends on delivery of clinical trials on time, within budget and conducted in a responsible, ethical manner, ensuring that a trials team is 'Research Ready' is an essential requirement.

3. The Case Study

3.1 Chapter Overview

This chapter describes the case study trial. I have redacted any obvious identifiable information. This chapter is written in a way to ensure that specifics about the trial are not presented – in order to protect those sponsor organisations and individuals involved from repercussions and reputational damage.

This chapter does not describe the case study trial by name, but does describe similar studies that have been done in the same disease population, in an attempt to describe the research environment and culture in which the research question was formulated, and the tradition of the research trials that had come before. This is important as there had been similar trials that had been done before, in the same disease population, testing similar investigational medical products – however, all of these encountered recruitment difficulties. For the purposes of the thesis, I have included references.

There follows a description of the trial itself – the inclusion and exclusion criteria and the unique design attributes that were included to simplify certain aspects of the trial, and to ensure that including participants in the trial and follow-up was less onerous for investigators – particularly those in external sites. In a similar vein, it was planned that a large proportion of the participants should be recruited through primary care – aspects of the trial design that were devised in order to facilitate this are also described.

There follows a section that describes the key events in the trial. This information was compiled from documents and correspondence that were made available to me through this research investigation. A series of illustrative timelines will describe the sequence of key trial events leading up-to trial closure.

3.2 Introduction

A randomized open label study comparing the effects of two drugs, available on all NHS drug formularies, on outcome in patients with a chronic health condition.

The trial was funded by a national clinical research funder within the UK. It attracted funding of over 3 million pounds (112).

The hypothesis to be tested was that, standard treatment (one of the drugs being tested – henceforth referred to as Drug A) had an adverse effect on symptoms and progression of the chronic health condition, leading to a worsening of symptoms, reduced quality of life, an increase in hospitalization and a higher mortality, compared to the newer agent (henceforth referred to as Drug B) that was being tested. The primary endpoint of the study was mortality.

The investigators aimed to enlist more than 250 study sites, including two large GP research networks, and through this, to recruit more than 3000 patients with the chronic health condition over a period of 5 years.

The trial came about at a time when there had been a number of randomized controlled trials of similar agents in the chronic health condition, however, all of these trials struggled to recruit to target – the largest of these that had been conducted in the UK (discussed in greater detail later in this chapter) were underpowered for morbidity and mortality (113-115).

The trial was designed to be ‘simple’ and reduce cost by minimizing administration, and keeping patient follow-up visits at a minimum. It was non-blinded, and the majority of follow-up was planned to be through postal questionnaires and telephone calls from a central monitoring and trials office. Patients or their next of kin were advised to inform the monitoring office in the event of hospital admission, and on an annual basis information about hospital attendance and medication changes would be collected from the patient’s primary care physician.

In order to ensure anonymity, rather than describing specific dates for the main trial events, I will describe the milestones in terms of month numbers, with the time point of the grant award being month 0, and the date of trial closure as month 40.

The trial was awarded the grant in 2009, contracts with the sponsor organisations were signed 11 months later, and the first patient recruited 2 years and 2 months after the grant was awarded, (Month 26). Recruitment targets were revised 9 months after the first patient was recruited, and due to failure to reach these targets by Month 40, the trial was closed down.

The aim of this thesis is to use this trial as a case study, to look at the issues that affect clinical trials in their first phases of set-up, and to undertake an analysis to look into what went wrong to make the trial fail as it did.

3.3 Background

3.3.1 Clinical decision problem

The chronic health condition being assessed as part of this trial affects one in five members of the population in their lifetime. Prognosis is poor without treatment, and the impact on quality of life is considerable. Despite changes in treatment over the last 30 years the condition is associated with significant mortality and morbidity.

This trial, and previous randomized trials that had compared similar drug agents, sought to examine the relationship between medication and morbidity and mortality in patients that had been diagnosed with this chronic condition. The trial was designed to compare two drugs – both medications that were off patent, and therefore low cost interventions. At the time of the trial the cost difference between products was £18.72 per patient per year.

3.3.1 Rationale for intervention in disease population

Professional guidelines with recommendations for treatment of patients with this chronic condition developed in the United States and Europe indicate uncertainty about the role of both of the study medications in the management of patients. A statement in the most recent national clinical guidelines for treatment of this chronic

condition document a ‘Gap in Evidence’ – identifying a need for further research into the roles of Drug A and Drug B within the disease population.

3.4 Previous research in this field

There have been a number of studies that have sought to examine the benefit of this class of medication therapy in patients with this chronic condition, and in total there have been 4 prospective randomized controlled trials.

Of note, the majority of these clinical trials did face recruitment issues. The first (Trial 1) was designed as a pilot study, NHS R&D-funded study specifically designed to find out whether a trial comparing medication treatment in patients with the chronic health condition was feasible. Recruitment took place between 1995 and 1997, and was closed to follow-up in 1998. In this first early trial, recruitment was slow. The subsequent journal article that was published (in 2004) as a report of the trial suggests that the slow recruitment could have been due to a reluctance of the investigators to randomize patients to either treatment arm of the study. The chief investigator of this trial had the impression that the local investigators responsible for recruitment felt that the treatment offered in one study arm to be superior to the other (112, 116). The experience of Trial 1 went on to inform the design of the subsequent 2 trials (Trial 3 and 4).

All of the studies that compared Drug A and Drug B in the chronic disease population faced recruitment difficulties, and the investigators for Trial 4 describe revision of sample size and recruitment target because of difficulties in achieving planned targets (117). Trial 4 had an enrollment rate of roughly 0.15 patients per site

per month that spanned over 176 sites, 11 different countries, and 7 years; additionally, in order to reach the intended power and target recruitment goals, over half of the patients in this UK based nationally funded trial originated from Europe or Argentina (117). The question arises as to whether there may have been a role for site based maintenance and support in order to ensure enthusiasm and consistent participant recruitment at external sites (118).

Trial	Enrolled	Planned sample size
Trial 1	279	
Trial 2	197	6000
Trial 3	1587	4500
Trial 4	2303	2860

Table 8. Recruitment to trials – the same participant population

The table above shows how the planned sample size differed from the numbers successfully recruited to the studies. The table below illustrates the baseline characteristics of participants included in each study, but also a summary of the inclusion and exclusion criteria. Each of these trials had very similar requirements, and were looking at the same disease population, and were assessing the impact of similar drugs.

This shows that the case study trial was a trial that had been designed at a time when Trial 4 (117, 119) had been designed and was actively recruiting, but had not yet reported its findings, on a background of a number of similar trials looking at similar interventions in the same disease population that had fallen far short of managing to recruit adequate numbers of participants. The Chief Investigator of the case study trial had designed Trial 1, and had the role of Chief Investigator for that study, and was author of the report of study findings (113, 116), he had also co-authored the

design and report of results, and taken a substantial role as a Principal Investigator in the Trial 3 (114, 115) which was terminated early due to slow enrollment. With the exception of Trial 1 (113), all other previous studies had involved recruitment of participants from more than one country.

The importance of highlighting previous trials with similar study designs is primarily because there was no separate feasibility work undertaken prior to the commencement of the case study trial – in the study protocol, previous trials in the literature were described as ‘pilots’ to the case study trial – and no additional feasibility work was planned.

“Trial 1” was a pilot, NHS R&D-funded study specifically designed to find out whether a trial comparing treatments in patients in the chronic disease population was feasible... “Trial 3” may also be considered a pilot for this study... Thus, lessons learnt from previous trials have been used to develop a much more robust and greatly simplified protocol.

(120)

Study	Number of Participants (n)	Design	Baseline Population Characteristics
Trial 1 (2004)(113)	279	Randomised, UK based, Multicentre, Open-label, Pilot study	Mean age 63 years; male 74 %
Trial 2 (2006) (121)	197	Randomised, Multinational, Multicentre, Double-blind placebo controlled study	Group 1: mean age 55 years; male 78% Group 2: mean age 62 years; male 89 %;
Trial 3 (2009) (115)	1587	Randomised, UK funded, Multinational, Muticentre double blind, double ‘dummy’ and open label controlled trial	Mean age 63 years; male 85 %;
Trial 4 (2012) (117)	2305	Randomised Multinational, Multicentre double blind, double ‘dummy’ controlled trial	Mean age 61 years; male 80 %;
Case Study Trial	87	Randomised, UK based, Multicentre, Open-label controlled trial	Median age 75; 75% male;

Table 9. Baseline criteria in similar trials in the same disease population

3.5 The Case Study Trial

The case study trial intended to compare two open-label medications in 3000 patients with the chronic health condition and on optimal medical therapy.. The hypothesis being that the differing modes of action of the two drugs being compared should translate into a clinical difference between participants receiving each drug, and impact on mortality and hospitalisations (112).

3.5.1 Primary and Secondary Endpoints

The primary outcome measure in the case study trial was all-cause mortality.

Secondary endpoints included

- Hospitalisation for the chronic health condition (time to first event)
- Sudden death or a vascular event (myocardial infarction, stroke, peripheral embolism, requirement for angioplasty or vascular surgery) using a time to first event analysis
- Total days lost to death or hospitalisation (all causes)
- Quality-adjusted years alive (QALY) using repeated measurements of EQ5D
- cost per QALY.

3.5.2 Subject Selection

The trial was designed with the purpose in mind to recruit from primary and secondary care in order to enroll a broad spectrum of patients

Inclusion Criteria

- Willing and able to provide written confirmation of informed consent
- A clinical diagnosis of the chronic health condition
- Currently in a stable condition on clinical examination
- Receiving medication for the condition for at least 6 weeks prior to inclusion
- Patients must have a telephone
- Patients must be willing to provide their personal contact details, those of their next of kin and those of their GP and hospital to the national coordinating office and be willing to be contacted by telephone by these staff.
- Patients must be willing to have hospitalisation and other serious events tracked through mechanisms including, in England, the NHS Central Register (NHSCR) and the National Office of Statistics and, in Scotland, The Registrar General's Office and NHS Information Statistics Division.
- Patients will be included regardless of aetiology of disease

Exclusion Criteria

- Plasma (central lab) Diagnostic blood tests with results not below the diagnostic level confirming the presence of chronic condition
- Lack of diagnostic tests that confirm presence of chronic disease condition.
- Presence of an alternative condition in the investigators opinion (test reports within the previous 12 months must be available)
- Evidence of organ failure on blood test (local lab)
- Intolerant of either of the study drugs or who have a contra-indication to such treatment will be excluded.
- Contraindications to either study drug treatment including
- Substantial, in the investigators opinion, with serious sequelae within the previous year,
- Endoscopically proven peptic ulcer within the previous 3 months. Patients must be on treatment if peptic ulcer diagnosed in previous year.
- Haemorrhagic stroke within the previous 3 months
- Known coagulation disorder (eg:- haemophilia)
- Full blood count suggesting iron deficiency (patients may be enrolled in the study after the cause of iron deficiency is or has previously been investigated and treatment has been initiated) (local lab)
- Platelet count <100,000 (local lab)
- Scheduled procedure that would require discontinuation of study medication for > 2 weeks (patient may be recruited after procedure)
- History of uncontrolled seizures or high risks of falls,
- Regular use of non-steroidal anti-inflammatory agents > 3 times a week
- Use of maintenance oral corticosteroids
- Women of child-bearing potential or who are breast feeding
- Patients with a history of lung conditions should not take part unless they

have taken the study medication previously without ill-effect.

- Patients with an indication for alternative drug treatment including
- current or recent (within 12 months) diagnosis of a different condition requiring alternative drug treatment
- prior embolic stroke
- mechanical prosthetic heart valve
- Patients requiring augmented medication due to recent significant organ damage
- Patients likely to die of something other than the chronic health condition are excluded
- Inability to walk without the physical assistance of another person (patients with walking aids are permitted)
- Other patients deemed unlikely to comply with the protocol.
- Women who are at pregnant or who could become pregnant. Women of child-bearing age should be taking reliable contraception (tubal ligation or implanted contraceptive)
- Inability to communicate in English. Non-English speaking patients who have a friend or relative who can translate or who have other access to translation may participate.

(112)

3.5.3 A Simple Trial

The case study trial was designed to be a simple and low cost trial. According to the trial protocol:

The trial is, in many ways, a conventional trial with the 'fat' cut off. The strategy seeks to identify all that is most important in a trial and those factors that are mostly administrative waste, contributing little scientifically. Some aspects of a trial might be important but expensive. Their real, practical and scientific value must be weighed carefully.

The trial design hinged on a ‘Central Monitoring Office’ -, staffed by administrators and a medical researcher, and would do the majority of trial participant contact. The duties of this office would include:

- Administration of participant randomization
- Confirmation of participant consent
- Participant follow-up (through post and regular phone calls)
- Administration of correspondence, blood tests and examination results from health professional analogous to each trial participant
- Recording of patient compliance to medication
- Administration of adverse event reporting
- Documenting of medication changes
- Data collection and updating of encrypted database with participant visit data

Design features that were included to make the trial simple included:

3.5.3.1 Un-Blinded treatment

Blinding creates increased costs to a trial because as specific drug supply generally has to be distributed from a central point – and the trial organisers describe how the use of these pharmacies can increase costs, cause inconvenience for patients – which may in turn reduce enrolment and reduces the ability of primary care to participate (112).

3.5.3.2 Follow up visits

For the purposes of the case study trial, in order to reduce costs, study visits were kept to a minimum. The only study related clinic visits were for enrolment and a six-month follow-up.

The patient would continue to be followed in the usual fashion by health care professionals involved in their day-to-day care, and copies of correspondence would be sent to the central monitoring office. Patients would then be contacted every two months, either by telephone, by post or by e-mail.

The majority of data would be collected by administration staff at the central monitoring office – patients would have contact every 2 months, this would take the form of either questionnaire packs being posted out, or phone calls where a medication list would be updated and a symptom questionnaire completed with the patient over the phone.

Schedule of Assessments

Visit	Baseline	Randomisation	2M	4M	6M	8M	10M	12M	etc
	Clinic	Phone	Post	Phone	Clinic	Phone	Post	Phone	etc
Medical History	Y								
Medication	Y		Y	Y	Y	Y	Y	Y	Y
Symptom Questionnaire	Y		Y	Y	Y	Y	Y	Y	Y
Oxygen Cost Diagram	Y		Y		Y		Y		
EQ5D	Y		Y		Y		Y		
Physical exam	Y				Y				
6MWT (optional)	Y				Y				
Blood tests	Y				Y				

6MWT = 6-minute walk test. EQ5D = European Quality of Life–5 Dimensions instrument

Table 10. Schedule of assessments

3.5.3.3 Randomisation

If patients agreed to participate, they would be randomly assigned to one of the trial medications using a computer-generated minimization strategy stratified by blood test results to minimise any imbalance in this most prognostically important variable. (This specific blood test is an important biomarker which can be linked to overall clinical prognosis (122))

The national monitoring office will first contact the investigator by phone (followed by confirmatory letter/e-mail) and then the patient to tell them what treatment they have been assigned to and how to get their prescription which may be obtained at any local pharmacy (prescriptions would be generally written by the patient's own GP)

3.5.3.4 High screen failure rate

Another major cost in conventional trials is the high screen failure rate. This cost had historically been borne by the investigator. The case study trial investigators thought that these high screen-failure rates acted as a strong disincentive to investigators and impaired recruitment. "Ensuring that all patients likely to benefit from the research can be enrolled improves recruitment and clinical relevance and ultimately reduces the overall cost of the trial." (112)

Therefore, the trials team aimed to keep entry criteria in the case study trial as broad as possible in order to capture the at-risk population encountered in everyday

practice in primary and secondary care and remove biases against recruiting older people and women who often have the chronic condition (This was through the usage of blood tests for disease specific levels in order to assess patient suitability for inclusion into the trial rather than imaging test evidence, which had been the norm in previous trials)

3.5.3.5 Adverse events monitoring

Patients or next of kin were asked to inform the central monitoring office if the patient was admitted to hospital (112).

In addition, on an annual basis, the central monitoring office would request copies of discharge and clinic letters, most recent blood tests, disease specific and imaging tests and major procedures from hospitals. From primary care physicians, medication, most recent heart rate and blood pressure and hospital referral letters.

3.5.3.6 Patient payment for participation

Patients were to be paid - unconditionally £5 for each completed smaller set of postal forms twice per year and £10 for a larger set once per year. These payments were to be made regardless of the medication that the patient was taking and was to include patients who had withdrawn from medication.

Patients were reimbursed reasonable travelling costs for the baseline and six month clinic visits.

3.5.3.7 Laboratory/Blood tests

The majority of these tests (such as the full blood count and renal function tests) would be organized and recorded through the patient's usual medical practitioner. The disease specific blood test analysis that would be used to assess patient's eligibility for inclusion to the study would take place in a central laboratory, and would be transported via Royal Mail, in a stamped addressed package.

3.5.3.8 Administrative costs

Costs for storage of documents and raw data, for example, Case Report Forms (CRF) that had been completed by investigating teams during patient interaction, either had the data manually inputted by central monitoring office trial administrative staff, and documents (such as hospital correspondence and ECG tracings) were scanned in and stored on secure computers, and original paper documentation was planned to be destroyed. This was done to reduce the burden of data storage and reduce the provision of space and maintenance that large volumes of paper based data would occupy.

3.6 Key Events in the Trial

Figure 6 shows a colour-coded routemap designed by the NIHR to guide users through the legal and good practice arrangements surrounding setting up and managing a clinical trial of an investigational medicinal product (CTIMP). It is

included here to help the reader appreciate the expected order and importance of different activities in the project management of large clinical studies.

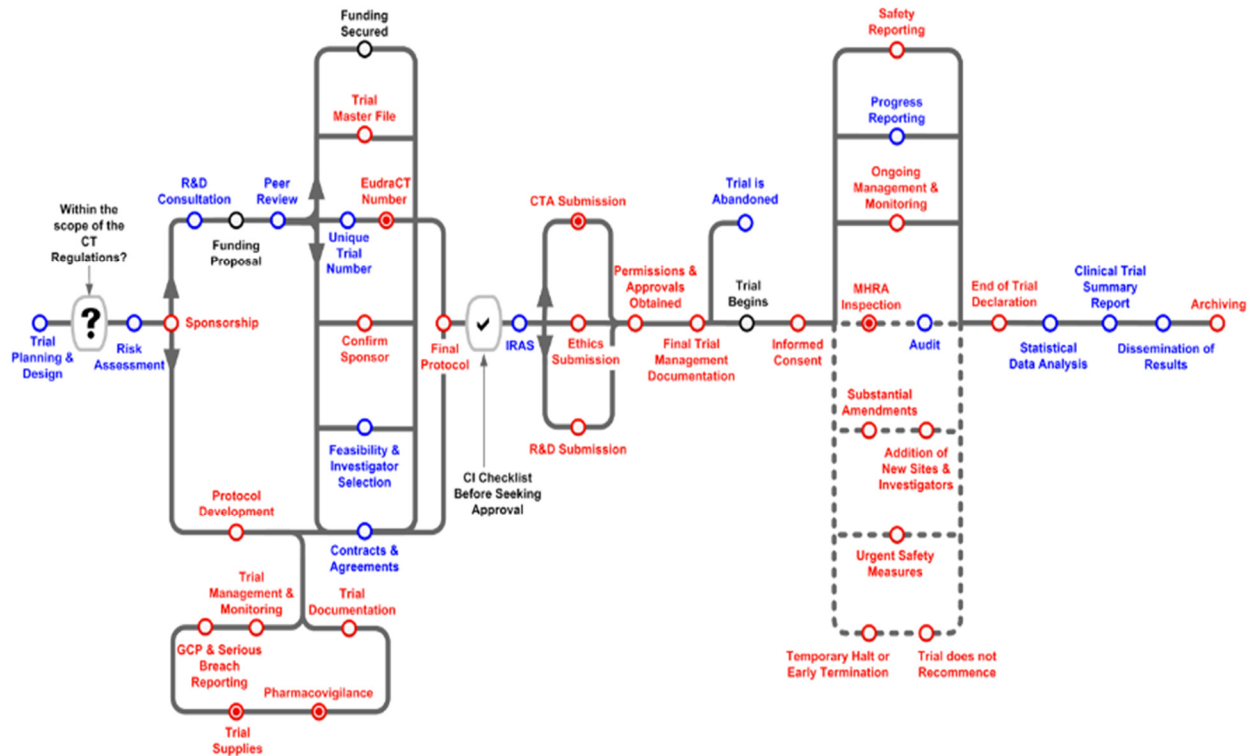


Figure 5. NIHR (National Institute of Health Research) Clinical trials toolkit (123).

The following summary and explanation of the key events of the case study trial were put together through a careful review of trials documentation, correspondence (which included emails), and diary information contributed by key members of the Trials Team – which included the trial project managers, representatives from CTU organization, sponsor HEI and hospital trust sponsor representatives and members of university and departmental management.

The case study trial was awarded a grant from a publically funded research programme in 2009. The grant award was over 3 million pounds

The Sponsor Agreement contract was signed in Month 11 between the funding body and the higher education institute. The first patient visit was at the end of Month 26.

There were concerns raised by the trial funders 2 years after grant award. Following the withdrawal of support from the Clinical Trials Unit in Month 26, an external review of the trial was commissioned by the sponsor in Month 29. The external review was undertaken by a representative from a Clinical Trials Unit (part of another higher education institution) and a number of concerns were raised.

In Month 33 a meeting of the Trials Steering Committee was called, following which a meeting was held between the Chief Investigator and the funder in Month 35, at which objectives and targets for recruitment were set. These included a target of 250 patients randomized and 100 active recruiting centres at the beginning of Month 40.

On the 1st day of Month 40 there were 87 patients randomized from 8 recruiting centres. The notice of closure was dated 13th day of Month 40 – by this point there were 102 patients recruited.

A number of key events affected the progress of the trial and caused it to deviate from the original budget projection and planned timelines. I endeavor to describe each of these areas in the following sections:

3.6.1 Appointment of Trial Project Manager

One of the first priorities for the commencement of the trial was the successful appointment of a Trial Project Manager.

In the grant application and at the commissioning stage, the trial was to be supported by a Clinical Trials Unit (CTU) – which was part of a higher education institution (HEI) separate to either of the sponsor organisations. It was planned that a trials manager there that would undertake an advisory and supportive role for the newly appointed local trials manager responsible for the case study trial. The CTU trials manager was contracted to advise on issues around the trial, for an estimated commitment of around 0.5 days a week, and there was a time period of 6 months built into the case study trial timeline for the recruitment of a local trials manager that would then undertake trials duties.

Funding was approved for 2 trials managers, one in a full time post for the full duration of the trial (5 years) and one for a period of 18 months – with the plan for the second trials manager to come into post once participant recruitment was well underway in order to support the first manager.

- Grant awarded Month 0
- Job description for Trials Manager finalised Month 10
- Project Manager (1) appointed 28th day of Month 12
- Project Manager (1) withdrew 30th day of Month 12
- Project Manager role re-advertised Month 13 – no applicants
- Commercial Research Organisation (CRO) approached in order to support trial and fulfill Project Manager role Month 13
- Decision to continue to advertise rather than involve Commercial Research Organisation Month 14
- Offer of secondment for temporary Trials Manager from CLRN Month 13 (to start Month 17)
- Recruitment agency approached Month 17
- Project Manager (2) appointed with 3 month initial contract Month 18
- Project Manager (2) did not have renewal of contract due to probity issues. Contract end Month 21
- Temporary Trials Manager (Project Manager (3)) from CLRN offered substantive contract Month 21
- Withdrawal of Clinical Trials Unit and associated project management support Month 25
- Clinical Research (Medical) Fellow appointed Month 33
- Second Project Manager (4) appointed Month 38
- Trial Closure Month 40

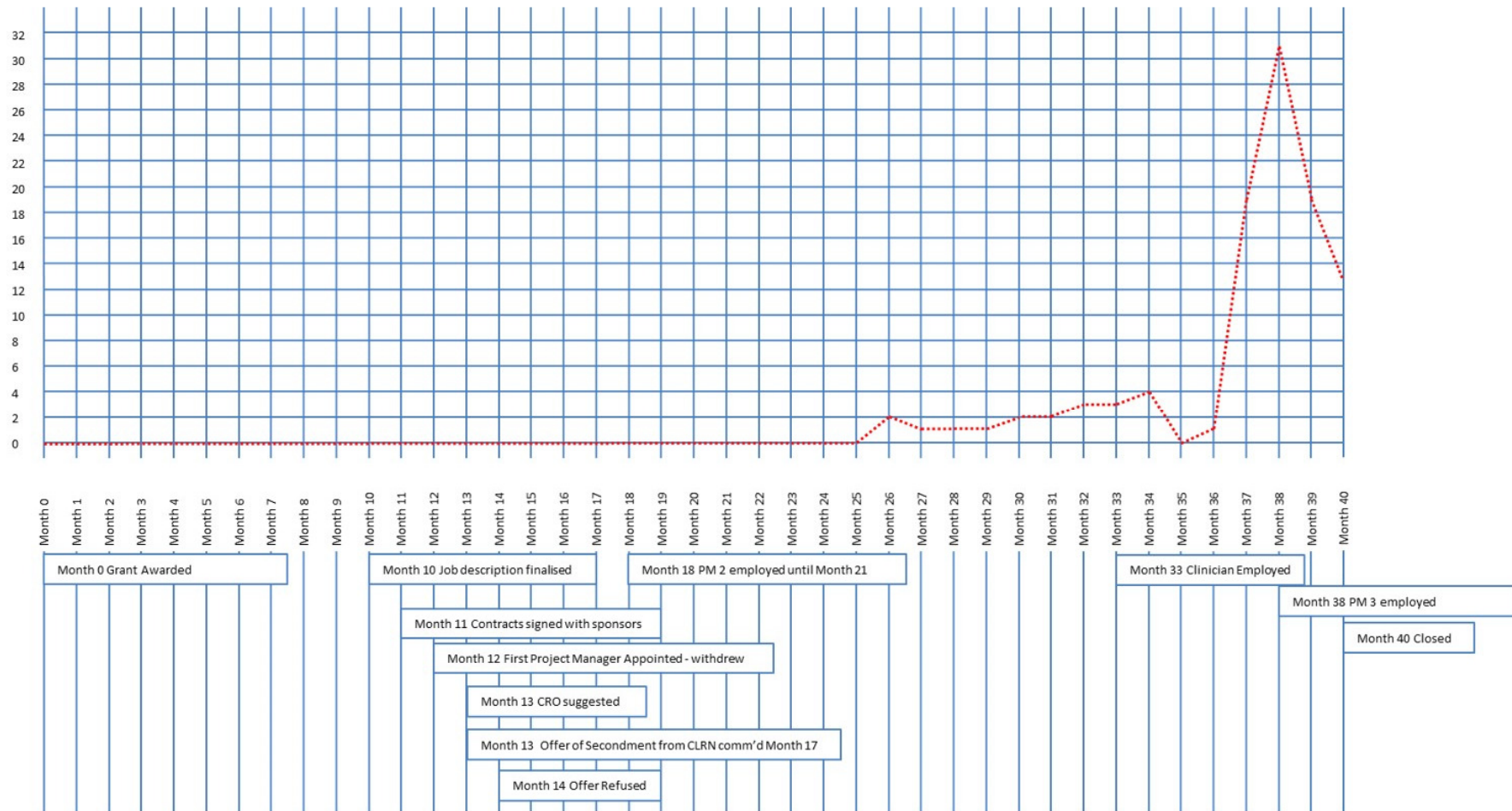


Figure 6. Timeline showing the progress of the Trial.

Appointment of the trial project manager vs number of patients recruited per month

3.6.2 Trials Management Events

A number of events occurred relating to the trials management. As per the timeline described above, one of the first challenges for the trials team was the appointment of a Trials Project Manager (At this point, there were no members of local staff that were dedicated on a full-time basis to trial related duties – the Chief Investigator had competing clinical and academic projects) This appointment suffered from severe delays, firstly due to the delay in finalising a job description, and then with recruiting and retaining a Trials Manager to drive the trial forward.

2 years after the grant was awarded, and before the first patient was recruited to the trial and randomized to treatment, two key co-applicants wrote to the funder, and copied to the university sponsor to inform them that they intended to withdraw their association and further involvement with the trial. The month after this, the Clinical Trials Unit also withdrew support.

Despite these setbacks, the first patient was recruited to the trial at the sponsor organisation in Month 26.

With the withdrawal of the Clinical Trials Unit and that of co-applicants, the higher education institution in it's capacity as trial sponsor, and with the support of the funder, commissioned an external review of the trial by a representative of the Clinical Trials Unit at another HEI. This took place in Month 28, and the report that was issued later in Month 28 noted the following issues:

- Staff seemed very inexperienced with running a clinical trial of this size and complexity.

Significant concerns with regards to:

- Willingness of Trials Team to accept the advice of the external Clinical Trials Unit (with reference to the CTU that had withdrawn support by this point)
- The financial resources available in the trial budget for trials management (The provision of the minimal support from the Clinical Trials Unit kept costs down for the trial, and there was little in the way of cost provision for additional support after CTU withdrawal.) There was insufficient budget provision for office accommodation for the Trials Management Team (and Central Monitoring Office) and equipment, such as computers, printers and scanners.
- Poor adherence to ‘Good Clinical Practice’ (GCP) by the Trials Team.
- Only one staff member had valid GCP training
- A previous project manager (‘Project Manager (2)’ described above) had taken home the ‘Trial Master File’ and it had been lost. The representative conducting the external review commented on the ‘lack of concern’ displayed by the Trials Team with regards to the seriousness of the issue.
- The Project Manager was working in isolation with little senior support. Concerns were raised with regards to the precariousness of the situation in that, should the project manager become sick, or have a period of absence for any reason – the progression of the trial would halt.
- The primary recommendation of the reviewer was that there should be support from a Clinical Trials Unit in order for the trial to survive.

There was a progress meeting held with the Trials Steering Committee – progress of the trial was discussed, and that recruitment had begun successfully despite the withdrawal of the Clinical Trials Unit.

In Month 35 there was a meeting between the Trials Team (Project Manager and the Chief Investigator) and the head of the funding body to discuss the slow progress of the trial and the rate of accrual of patients. At this meeting recruitment targets were discussed and revised. The Trials Team did not revise targets that were set at the planning stages of the trial, and agreed to targets of 250 patients recruited to the trial, and 100 actively recruiting centres by 1st day of Month 40.

In Month 37 the heads of the sponsor university research department were informed by the funder that the trial had been under review, and that recruitment targets had been agreed to. They were informed that the funder intended to close the trial and withdraw funding should these targets fail to be met.

In the same month, the head of the University research department and the section head of clinical research met with the Chief Investigator for the trial. They pledged their support, and nominated a professor within the university research department to take over the day-to-day running of the trial, and to support the Trials Management Team. This change in management came about in Month 37.

In Month 39 the first Investigator meeting was held. Prospective recruitment teams and investigators from external sites were invited to workshops and given information about the trial in order to promote patient recruitment.

On the 1st day of Month 40 the number of patients and the number of actively recruiting centres had failed to reach target, so the trial was closed.

- Grant awarded Month 0
- Contract signed between sponsors (Hospital trust and HEI) Month 11
- Withdrawal of co-applicants Month 24
- Withdrawal of Clinical Trials Unit Month 25
- First patient recruited and randomized Month 26
- External review Month 28
- Meeting of the Trials Steering Committee Month 33
- Meeting with funder to set Recruitment targets Month 35
- Trials management taken from Chief Investigator to Professor HEI clinical research department Month 37
- Investigator Meeting Month 39
- Trial Closed Month 40

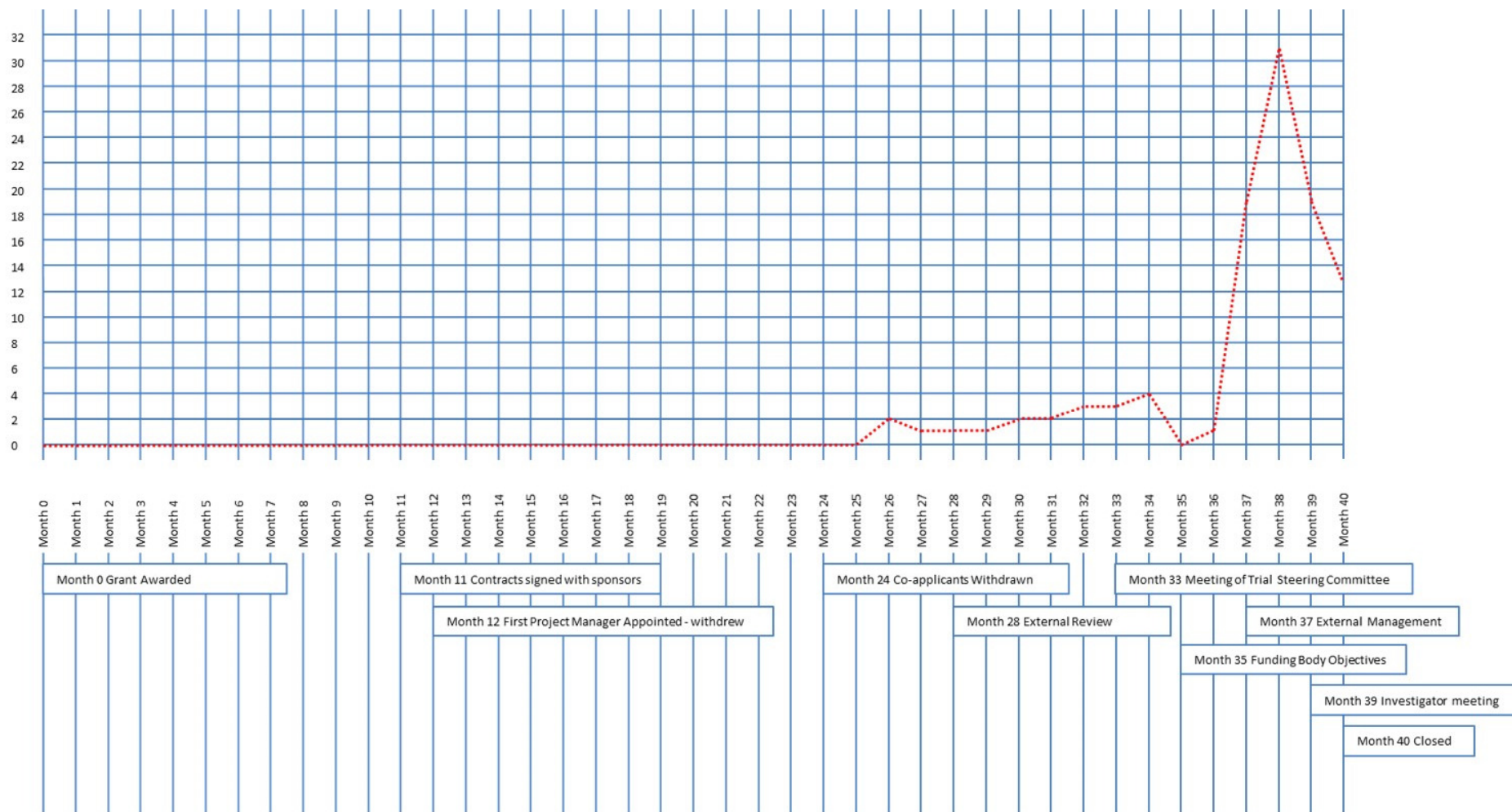


Figure 7. Timeline showing the progress of the trial. Trials management events vs number of patients recruited per month

3.6.3 Establishment of Database

The establishment of a secure database was essential to the design of the trial. As part of the plan to reduce on administrative and storage costs the vast majority of the data collected as part of the trial was planned to be scanned in, or manually entered into a secure database, linked to secure servers.

The establishment of the database run into delays and, following the trial closure, it was found to have been in excess of original budget forecast that had been planned and submitted as part of the trial plan. It was also in excess of the original amount that had been quoted by the successful database provider when the original database product was put out to tender. The main reasons for this will be explored later on in this thesis, but maintenance and updating and revising the database properties late on in the project, and adjusting functionality were both reasons that were documented in communication by the database providers and project managers as reasons why the budgets overran.

- Grant awarded Month 0
- Contract signed between sponsors (Hospital trust and HEI) Month 11
- Functional requirement of the database written Month 13
- Tenders submitted Month 18
- First patient recruited to trial Month 26
- Database go-live date Month 35
- Trial Closed Month 40

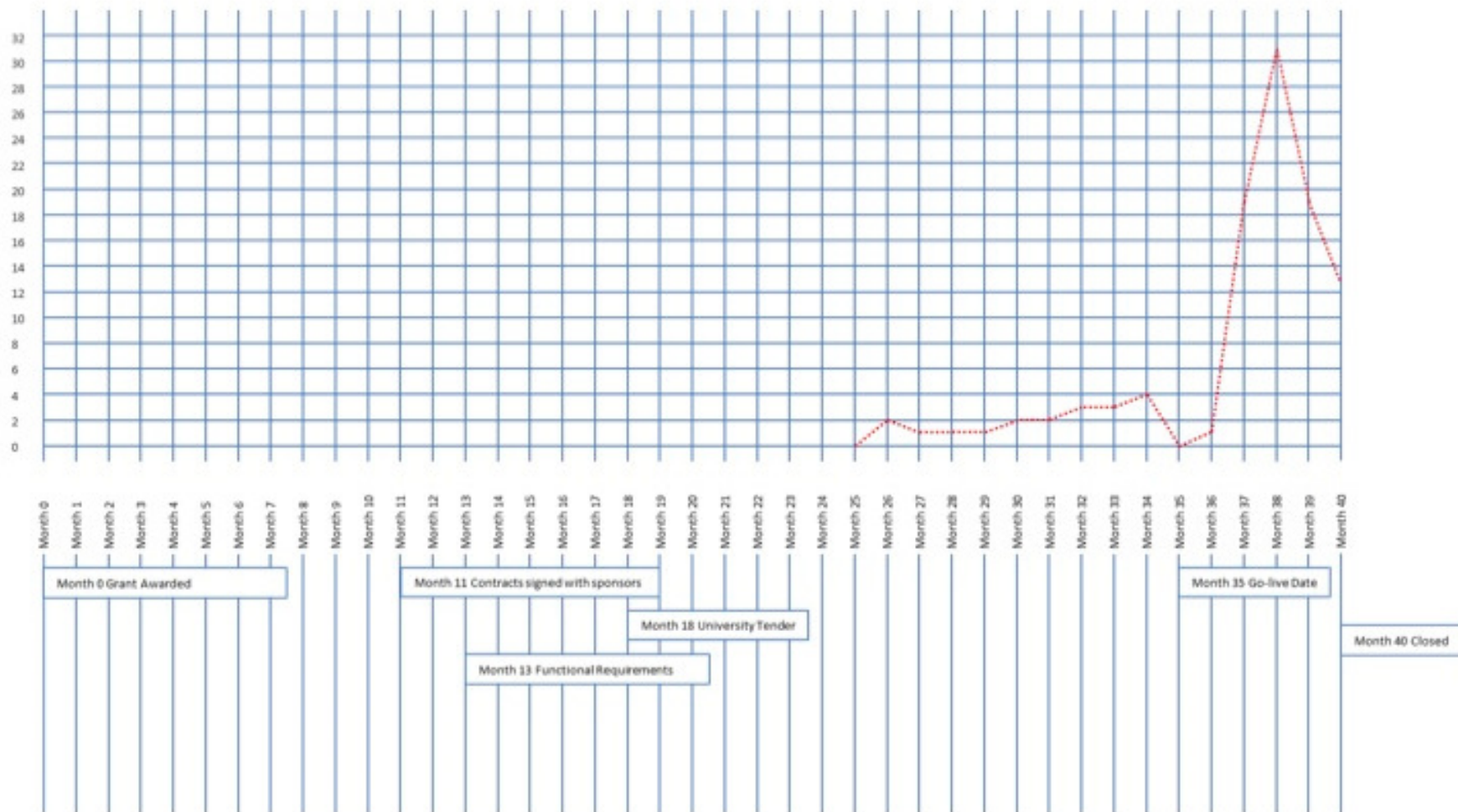


Figure 8. Timeline showing the progress of the trial. Establishment of the database vs number of patients recruited per month

3.6.4 Participant Recruitment

Trial Participant Recruitment began with the first patient being included and randomized to receive trial therapy in Month 26.

The first participant to be included and randomized that had been recruited from an external site had their initial visit in Month 35. They could not be included and randomized until Month 36 as all trial recruitment was held for 2 months – from Month 34 to Month 36.

The suspension of trial recruitment for 60 days was due to concerns from an ethics committee. The trial was resubmitted to ethics as part of routine procedure at the time – because the inclusion of new external recruiting sites involved a substantial amendment of the trial protocol. As part of the review of the trial protocol, committee members raised concerns with regards to a certain part of the protocol (which had already successfully been through the ethical approvals process on two previous occasions) that involved the transport of blood samples from external sites to a central laboratory for analysis via conventional Royal Mail post.

In Month 37, following the introduction of a different professor in a management role for the trial, there was an increase in the number of patients recruited into the trial, however, failure to reach the targets set by the Chief Investigator and funder meant that the trial was closed in Month 40.

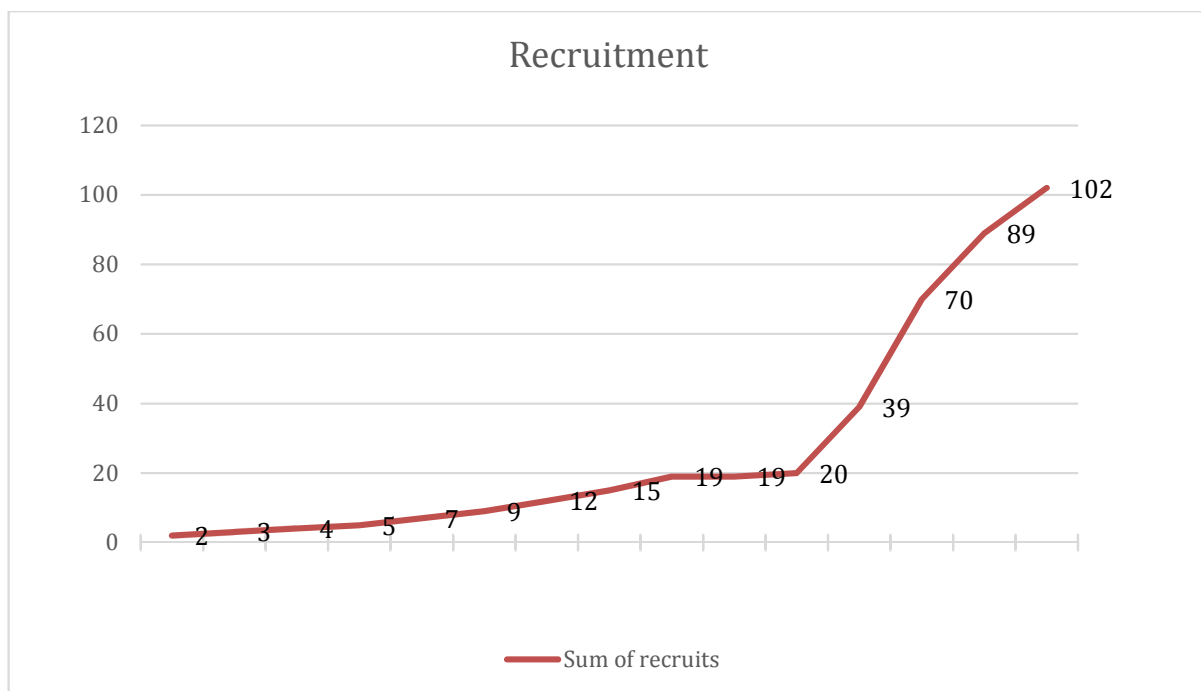


Figure 9. Sum of total patients recruited to the trial from Month 20 to Month 40

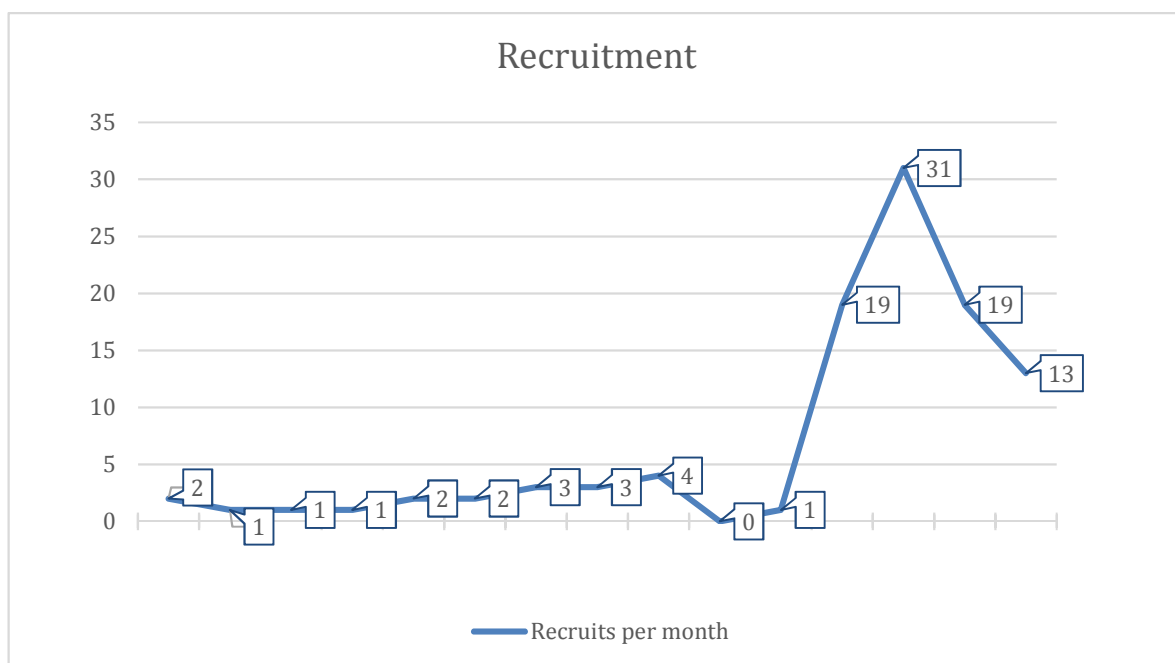


Figure 10. Recruitment of patients per month. (From Month 20 to Month 40)

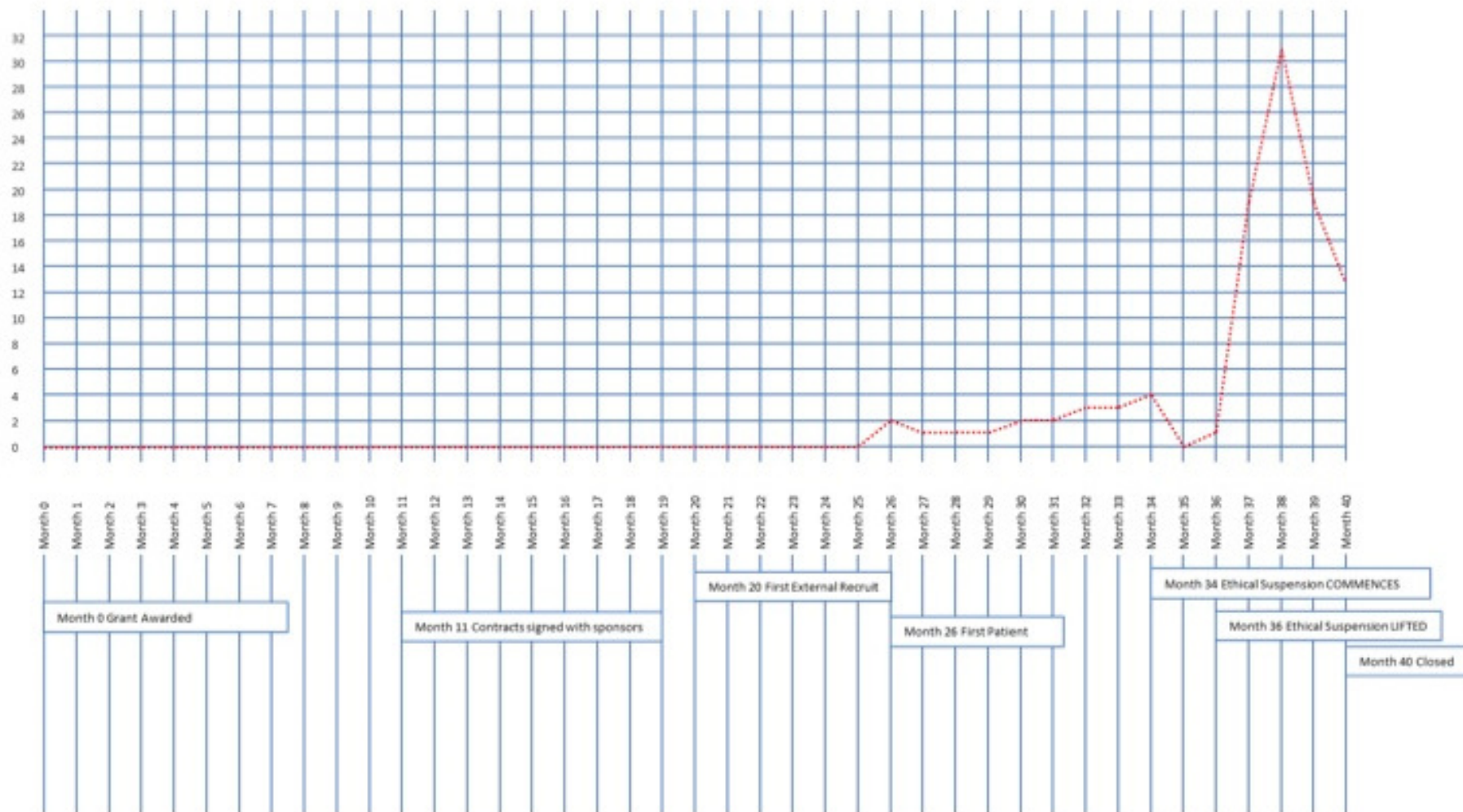


Figure 11. Timeline showing the progress of the trial. Recruitment events vs number of patients recruited per month

3.7 Conclusions

The case study trial was, like many other trials, subject to a great number of setbacks in progress. There were a number of issues – more of which will be discussed in later chapters – that meant that it was particularly precarious at times.

Delays in the establishment of a trials team meant that there were subsequent delays in the establishment of permissions and therefore recruitment of patients into the trial.

There was minimal support planned into the trial design from an established Clinical Trials Unit, and then when that was withdrawn without budget provision for getting another Clinical Trials Unit involved, once again this meant that trial progress was slowed again.

Negotiation with the funding body and the agreement of targets for recruitment that were, in the end, impossible to achieve, may reflect a Trials Team that were optimistic, and perhaps inexperienced.

In the end, the suspension of recruitment by ethics at a time when there was little in the way of reserve, or potential opportunity to ‘catch up’, or make up for that lost time, meant that the trial truly did fail to achieve the targets that the Trials Team had hoped for, and that this “Simple trial with the fat cut off” was halted and closed.

4. Theoretical approach to the case study

4.1 Chapter overview

In this chapter I describe the theoretical frameworks and models that I have used to order and interpret qualitative data in Chapter 7. I have used two areas of literature from which to derive the frameworks used.

The first relates to the proper conduct of trials, and interweaves two frameworks, which bear on the efficient and ethical conduct of trials. The ‘International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice’ (ICH-GCP) is an ethical framework which details requirements for designing, conducting, recording and reporting clinical trials that involve people (37). Robinson and Cook’s Clinical Trials Risk Management descriptive framework for understanding potential sources of failure in the design and conduct of clinical trials(11). Both ICH-GCP and Robinson’s framework focus on undesirable events to be avoided if a project is to be successfully conducted.

The second body of theory is James Reason’s model of organizational accidents, an explanatory middle-range theory derived from psychology, human factors and cognitive science. The model classifies types of failure and hypothesizes links between each and with undesirable events (mistakes, violations or unsafe acts). An explanatory middle-range theory seeks to identify relations between concepts, and to explain the extent to which one concept is related to the other.

As ethical and descriptive theories, respectively, ICH-GCP and Robinson's framework do not answer 'how' and 'why' questions. They will provide an important first level of abstraction from my raw data into higher order descriptive categories – types of individuals, groups, situations and events, but do little if anything to link those categories in a causal model. However, they provide the essential descriptive framework for the context of my case study – the failure of a clinical trial. Then, James Reason's explanatory model enables us to see links between the actions of individuals and groups, situations, or events. In short, it enables us to better describe why a trial fails. This model is situated in a much larger literature, and has been utilized extensively in industry, and as part of clinical risk management and patient safety within healthcare settings.

This thesis demonstrates the first application of Reason's model of organizational accidents in a clinical trials project management setting. The justification for using this theoretical model is discussed in the next section.

For the purposes of this research, I am conceptualizing the premature closure of this trial as a serious incident – a form of adverse event, or accident: Something that generally should not happen if all conditions are favourable and the trial is well managed, i.e. an event that has occurred due to error or a failure to apply an accepted strategy for prevention. Although high profile cases of catastrophes such as aeroplane crashes (124), the Challenger disaster (125), the accident at Chernobyl (126), and adverse events in hospitalized patients (127) may at first seem to have little in common with the adverse event examined in this thesis (the failure of the

clinical trial), they are linked by the fact that organizational structure, process, task and environmental pressure are almost always implicated in their production (128).

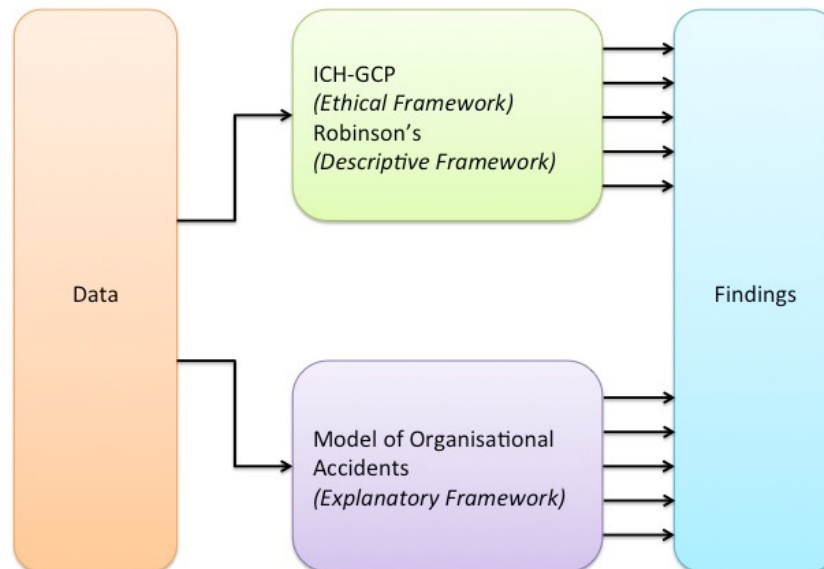


Figure 12 Frameworks to order and interpret qualitative data

The use of the ICH-GCP and Robinson's framework helps to conceptualise the key elements of the trial, and to direct the focus to those parts of the trial process that are at most risk of accident, or things going wrong. The use of Reason's Model of Organisational Accidents helps with understanding why these things happen, and what can be learnt.

4.2 The investigation of critical incidents in healthcare

Since the mid 1980's several interdisciplinary research groups have begun to investigate the human and organizational factors affecting the safety of healthcare provision (129). Concern about the frequency with which adverse events in healthcare occur continues to rise (130) however, a sociological perspective suggests

that many adverse events that occur are due to the failures of the system rather than individual failures (131). Many of the errors, accidents and adverse events that occur in a healthcare environment are rooted in features of the organisation (132). Complex organisations such as that of healthcare, or as in this case, that of a clinical trial environment, involve a multitude of different process steps, human interactions and individual actions. Given this complex environment, comprised of human individuals, the risk of error is considerable, and it has long been accepted in the field of organizational sociology that mistakes of all kinds are a normal part of work (133), and no matter how hard we try, certain systems, particularly with interactive complexity, are bound to fail eventually (134).

Early psychological contributions to the understanding of accidents were based on ‘accident proneness’, or the idea that some individuals have personality characteristics that make them more prone to accidents (135). This approach focused attention on the individual involved, allowing the responsibility of error to be delegated to those that do the job (136) this became known as the ‘Person Centred Approach’. The ‘blame culture’ which tends to surround adverse events in organisations shows a tendency to locate the sources of accidents primarily in the behaviour of individual staff members, ascribing blame for error to the ignorance, incompetence or immorality of an individual rather than in the social organization of work. This ties in to the belief that should individuals be dismissed or retrained that the risk of another accident disappears. This approach does not do justice to the multi-determined nature of most incidents in complex systems (38) and misses the complexity and multilayered causes of behaviours and outcomes. The danger would

be that should a culpable individual be found and the investigation closed, the opportunities for organizational learning may be missed.

In an organizational culture where individuals are blamed for adverse events, there is the possibility that such events would go unreported whenever possible. This means that the organization would never have a clear grasp of the nature and safety of the threats to safety that it faces (137). The systems approach to risk management adopts a more sophisticated perspective, focusing not only on the individual, but also on the role of organizational factors (40), acknowledging the fact that people do not act in isolation, that their behaviour is shaped by circumstances and the physical, social and organizational environment in which individuals operate (129, 138).

Incident investigation that takes into account the distinction between errors and violation, the need to establish proximal and distal causes and organizational issues such as deficiencies in training, supervision and poor communication as potential causal factors are more likely to lead to organizational learning (139). Studies of organisations where failures would lead to major disasters (140, 141) such as aircraft carriers and the US air traffic control system show that organisations that manage to operate reliably as a routine share a number of features (131). One of the most important distinguishing features of high reliability organisations is their collective preoccupation with the possibility of failure. They expect to make errors and train their workforce to recognise and recover them. They utilize the outcomes of incident investigation and continually rehearse familiar scenarios of failure and strive hard to imagine novel ones (40).

4.2.2 Techniques for the investigation and analysis of critical incidents in healthcare

The analysis of adverse outcomes and critical incidents in healthcare is increasingly performed in order to reduce the incidence of harm, and to learn from accidents and near-misses.

Below I compare 6 core techniques that provide a useful foundation for making comparisons between approaches

1. Australian Incident Monitoring System (AIMS)
2. Confidential inquiry method (CIM)
3. Critical incident technique
4. Significant event auditing (SEA)
5. Root cause analysis (RCA)
6. Model of Organisational Accidents (MOA)

1. Australian Incident Monitoring System (AIMS)-

Provides a mechanism for reporting any incident (that has actually occurred, or a near miss) via a single standardized form. It is designed so that incidents are reported in 'real time'. The coding of the information provides ways of understanding the underlying causes of the incident, analyzing the contributory factors in order to identify problems and best place remedial action. This is achieved through the individual who is self-reporting the incident coding the incident on the form based on whether it was their impression that there were 'System based factors contributing to the incident', whether there were 'Factors to minimize the outcome' and whether

there are any 'System based corrective strategies' (142). Most publications are from Australia and in anaesthetics/ITU medicine

Runciman's (AIMS) (142) model allows the reporting of an error anywhere in the chain from intention, through planning action to outcome and draws on Norman's slip/mistake distinction (143), Reason's categories of knowledge based mistakes, rule based mistakes, and skill-based slips and lapses (38), along with conceptual framework put forward by Rasmussen (144). There are several examples in the healthcare literature where this method has been used (145, 146).

However, the main drawback with this method is that it centres around self-reporting of incidents by front line staff, and typically the data are analysed by individuals working outside the organization. Although the system ensures anonymity, the level of detail in the information provided is dependent on the individual reporting. Only one type of data is analysed (secondary documentation) with no opportunity to seek further information because of informant protection, making this method unsuitable for the case study examined in this thesis.

2. Confidential Inquiry Method (CIM)

The application of an audit approach to assess healthcare quality. Centred around identifying all incidents of interest (usually deaths) in a specified population over a specific time period. Has been used in the UK for the investigation of suicide in people with mental illness (147, 148), the investigation of stillbirths and deaths in pregnancy (149), and avoidable deaths in those with stroke and hypertension (150).

The underlying theoretical basis for audit is that healthcare staff and managers want to perform well, but have little appreciation of the standard of their own performance (151). The findings of confidential enquiries are quite remote from individual cases, and they tend to focus on clinical issues rather than context and the overall environment where adverse events have occurred. The audit approach across a large number of individual incidents would make this method unsuitable for this individual case study.

3. Critical Incident Technique (CIT)

The critical incident technique provides a research based approach for the investigation and analysis of clinical incidents. First described by Flanagan in 1954 (152), it allows information on causes and contributory factors to emerge as cases are gathered (151).

Most examples of this technique and its use have been in the field of anaesthesia, through the work of Cooper et al from 1978 (153) which focused on anaesthetic ‘mishaps’ and examined issues around that of human error (154, 155).

Early studies centred around interviews with members of staff, the nature of which was not well described. Cooper describes the search for causal patterns as ‘primarily an intuitive process’ (155). Later examples have used questionnaires, where few details have been given as to the methods behind how each critical incident was assessed (156). The technique depends on causal links between incidents being recognized as individual cases are gathered, and has validity as a qualitative research method utilizing grounded analysis (151), however, for the purposes of this thesis

where one single case study is analysed in critical depth, this method would not have the correct fit.

4. Significant Event Auditing (SEA)

SEA involves reflection on a single case or event, usually with an adverse outcome (157). It is defined as a process in which individual episodes are analysed in a systematic and detailed way in order to understand how to make future improvements (158). In practice, SEA meetings are conducted in groups, in the form of facilitated case discussions, and forms a work-based reflective activity (159). Standards are judged by peer review and learning is usually from a single or small series of cases (160).

There is no explicit links between this technique and the theories of accident causation (151). SEA is promoted as a tool for quality improvement in the general practice setting, and has a role in the revalidation process for doctors in general practice (161). Many potential benefits to this method have been documented, such as the ability to prompt audit or to improve commissioning (162). However, problem analysis is at a superficial level – often identifying issues at the individual or process level rather than a systemic or organizational level. This makes SEA an unsuitable tool for use in the context of this case study where multiple organizations are involved and the level of analysis beyond that described here would be needed.

5. Root Cause Analysis (RCA)

A retrospective approach to error analysis, root cause analysis (RCA) was originally developed as a methodology to investigate serious accidents in industry (38),

becoming popular in the 1970s as a problem-solving tool used as part of the Toyota production system (31) . Since then this method has been increasingly used in healthcare to investigate adverse events (163-166)

RCA is essentially a total quality management tool. It is a systematic approach that drills down to identify the basic reasons for a problem – the ‘root cause’ (166). The analysis digs deeper by asking ‘why’ questions until no additional logical answer can be found, and identifies changes that could be made to systems and processes to improve performance and prevent a similar incident in the future (151). Classic RCA is not based on any particular theory of human error or system failure, although the NHS improvement Serious Incident Framework model of RCA (167) does bring links from Reason’s model of organizational accidents (40) and Rasmussen’s Skill, Rule and Knowledge model (144).

RCA is directed towards identifying weak points in systems and processes, and focuses on how to improve processes rather than blame an individual. In the early stages of this research, my initial approach to the case study was that of RCA, and the interview questions that I first piloted were based on the ‘5 Whys’ structure. However, although there is evidence of this approach working well for straight-forward process orientated problem solving (168), It works less well in complex systems with many influencing factors and points of causality (166). Although it can lend an insight into what happened, and what caused the incident, if the overall purpose is to achieve a safer organization or system, RCA is less likely to be a good fit (32, 163, 169).

6. Model of Organisational Accidents (MOA)

The model of organizational accidents developed by Reason (170, 171) illustrates how fallible decisions made at the higher levels of management structure or latent failures have an effect at departmental levels, where task and environmental conditions can promote unsafe acts.

Key papers have shown studies that have been conducted in a number of different healthcare settings using this model (139, 164, 172). Investigations have depended on gathering and analysis of interview data, with confirmation of events from written records.

MOA focuses on improving systems and the working environment rather than blaming individuals (151). The approach identifies a range of weakness in systems, and can identify where interventions may need to be targeted – sometimes at several levels in the hierarchy of an organization (173, 174). The use of this model for the analysis of the data gathered as part of this research for the case study examined as part of this thesis is most suited to answering the ‘Why’ questions. The framework that has been collated from the project management literature, and guidelines for practice (ICH-GCP and Robinson) are used for the ‘What’ and ‘How’ questions.

In summary, for the purposes of the case study research project in this thesis, the initial approach and that used for the formulation of interview questions was that of a root cause analysis. The approach then used for the purposes of the interpretation and the analysis of the findings was that of using theoretical frameworks described in this

chapter, and utilizing the model of organizational accidents, and explanatory theory better suited to the complexity of the system.

4.3 Clinical trial risk management and ICH GCP

4.3.1 Section overview

This section synthesizes the ethical framework, ICH-GCP, and Robinson's descriptive Clinical Trials Risk Management framework. Both of these lend a way of looking at the data obtained from interviews and ordering it in a way that it is possible to see the risks that the trial encountered, and an appreciation of the chronicity of events. Both the descriptive and ethical parts of the above framework will form the basis of themes by which the results will be ordered – this will be described in greater detail in chapter 6.

4.3.2 Risk Management in clinical trials

Risk management practices are indigenous to many industries and organisations. It is also an important tool that is used by the armed forces, integrated into military training and operations management systems. It has a significant role in the field of patient safety within healthcare. It allows leaders to make informed decisions about courses of action, and to provide reasonable alternatives for a task without compromising safety and standards.

The Association for Project Management describe risk as 'An uncertain event or set of circumstances, which should it occur, will have an effect on the achievement of

the project objectives' In other words, a risk may be either a positive 'opportunity' or a negative 'threat'.



Figure 13 Risk event diagram

The risk profile of a clinical trial will evolve as the venture moves through the definition, planning, implementation and close-out phases. Typically, the uncertainty will be highest before the initiation of the trial, with estimates with regards to the outcome becoming increasingly accurate as the project continues.

4.3.3 Phases of a clinical trial

In order to understand which risks are encountered in a clinical trial, and at which point in time, the clinical trial is first divided into phases – Definition, Planning, Implementation and Close-out of the trial. In this case study evaluation we will be examining the first three phases, as the trial was closed early – during the implementation phase, and before participant recruitment was complete.

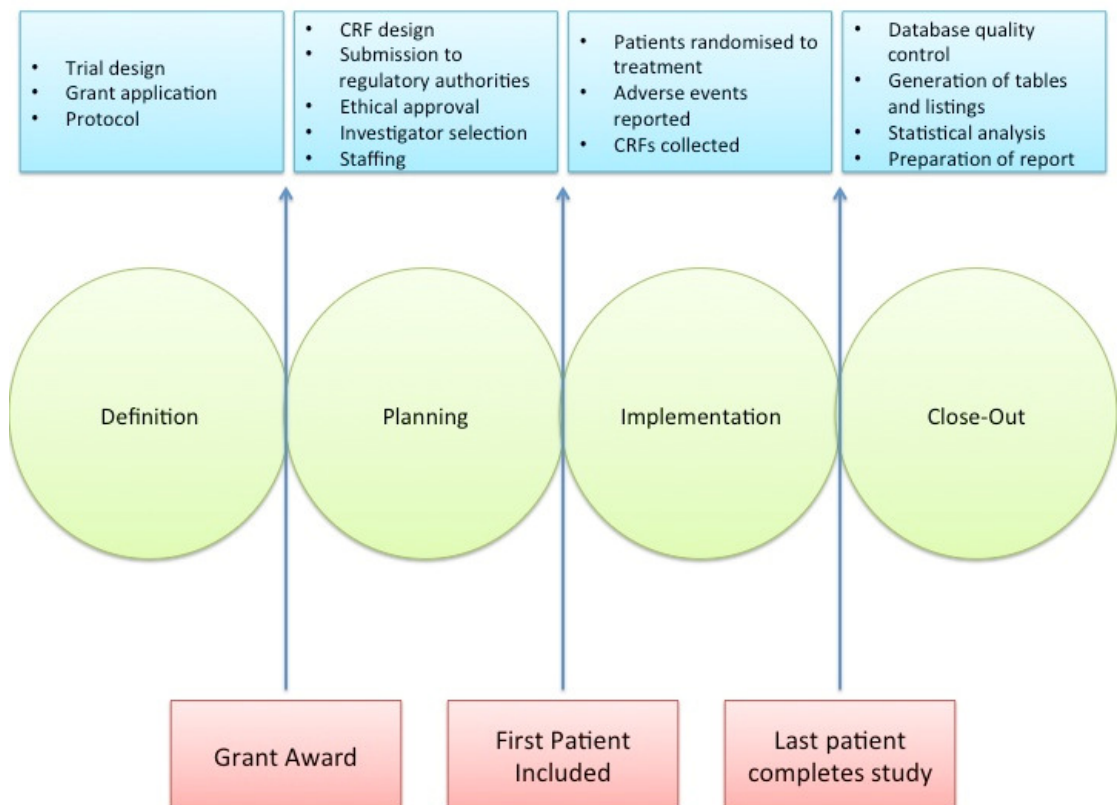


Figure 14: Phases of a clinical trial

Figure 14 describes the phases of the clinical trial and how each phase is divided – the phase up to the point at which the grant is awarded by a funding body is the ‘Definition Phase’ The period of time up to the inclusion of the first trial participant is the ‘Planning Phase’ and that up to the last patient makes their last study commitment is the ‘Implementation Phase’ (11).

Naturally, through the duration of a trial, there will be aspects that can be directed by the project team, and factors that are outside their influence. The risks in a project may be derived from two sources: the first, such as political forces and changes in the law, are known as external risks. The second consists of the uncertainties existing in the project itself, which are called internal risks (175) – examples of these could

include risks caused by staffing, or human resources shortage. Long projects are more at risk of external factors than short ones as predicting them is more difficult the further we look into the future (11).

From the clinical trials risk management literature (11) the phases of a clinical trial were identified (as discussed in the introduction) each of which can be vulnerable to particular risks. The data was coded according to these areas. These are discussed in further detail below.

4.3.4 ICH-GCP

Additional consideration was given to violations of ‘Good Clinical Practice’ – ICH-GCP is an international ethical and scientific quality standard for designing, conduction, recording and reporting trials that involve the participation of human subjects. GCP aims to ensure that studies are scientifically authentic and the clinical properties of the product or treatment under investigation is adequately reported. GCP guidelines include standard on how clinical trials should be conducted, and include a definition of roles and responsibilities of each clinical trial stakeholder (including clinical trial sponsors, clinical research investigators and monitors). High standards are a requirement in order to assure quality – this means that comprehensive documentation for clinical protocol, record keeping, training and facilities (including a high standard of computers, data security and software specification) is essential. Regular trial inspection ensures that these standards are maintained.

Where each phase of a clinical trial is discussed below, those ICH-GCP considerations that apply to each section will also be discussed. The responsibilities of key individuals and organisations involved in a clinical trial are divided into funder responsibilities, sponsor responsibilities and investigator responsibilities. As part of the trial examined here, the sponsor responsibilities were divided between a hospital trust and a university, and the position of investigator refers to the Chief Investigator of the trial.

Funder Responsibilities: Organisations that fund research have a responsibility to ensure that it is a proper use of the funds they control and provides value for money. The main research funder plays a critical role in assuring the quality of a study. It will normally take the lead in establishing that the research proposal is worthwhile, of high scientific quality, and represents good value for money (176).

Sponsor Responsibilities: The sponsor of a trial is an individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study. The sponsor is responsible for ensuring before a study begins that arrangements are in place: for the research team to access resources and support to deliver the research as proposed; and to allocate responsibilities for the management, monitoring and reporting of the research. This trial had two co-sponsors, the responsibilities that each organization is accountable for is described below:

Responsibilities of care giving organization: Hospital trust

- Arranging for an appropriate person to give permission for research involving their patients, service users, carers or staff, before the research starts.
- Ensuring any such research is conducted to the standards set out in this research governance framework.
- Requiring evidence of ethical review before recruitment to any research that affects their duty of care.
- Before recruitment to trials with medicines, requiring evidence of a positive ethical opinion and a clinical trials authorisation.
- Retaining responsibility for the care of participants to whom they have a duty (177).

Box 1 : Key responsibilities of the Care Giving Organisation

Responsibilities for employing organization: University

- Promoting a quality research culture.
- Ensuring researchers understand and discharge their responsibilities.
- Ensuring studies are properly designed and submitted for independent review.
- Ensuring studies are managed, monitored and reported as agreed, according to the protocol.
- Providing written procedures, training and supervision.
- Taking action if misconduct or fraud is suspected (177).

Box 2 : Key responsibilities of the Employing Organisation

Investigator Responsibilities: The Chief Investigator is the person who takes overall responsibility for the design, conduct and reporting of a study if it is at one site; or if the study involves researchers at more than one site, the person who takes primary responsibility for the design, conduct and reporting of the study, whether or not that person is an investigator at any particular site (176).

Definition Phase

There are a sequence of activities which constitute a clinical trial, and these are common between projects – the main operational stages through which an entire trial

will pass have been defined by Robinson and Cook in the textbook ‘Clinical Trials Risk Management’ (11).

Table 11: Phases of a Clinical Trial

Phase of Trial	
Definition	• Clinicians and statisticians will map out the most efficient experimental approach to obtain required information relevant to the treatment’s development status • Consideration given to scientific methodology, study population, standard medical practice and expectations of the regulatory authorities
Planning	• The trial plan is translated into a protocol that is acceptable to ethics committees and regulatory authorities and is compliant with ICH-GCP guidelines • Case Report Forms (CRFs) are designed and printed – these are forms in which raw trial data is collected • Project managers will compile a list of potential investigators and investigator sites – part of this process will involve evaluation to ensure that there are adequate resources to ensure responsible study conduct • Site initiation with all study sites takes place in order to ensure all sites are up to date with trial procedures and sites are set up adequately with reasonable facilities and access to necessary patient population in order to conduct the trial
Implementation	• Once the first trial participants commence treatment, completed CRFs are collected and information transferred into a database. • Patient consent, data recording and protocol adherence are monitored in order to ensure satisfactory allegiance to trial procedures • An independent quality assurance team will audit the trial for GCP compliance by inspections of investigational sites and in-house activities

Within the definition setting, the grant application team agree to the objectives, quality requirements, timelines and budget. Description of the project scope, geographical distribution, and lines of communication are discussed. Occasionally, in order to be able to predict how a trial will progress, and to support potential cost and recruitment projections, a feasibility survey or pilot study is required (A pilot study is a small-scale test of the methods and procedures to be used on a larger scale) (178).

This may help in combining previous experience accrued from past projects with the anticipated requirements in order to ascertain whether previous methodology is predictive of success (11).

The following tables describe internal and external risks that may be encountered as part of the ‘Definition Phase’ of a clinical trial. Both opportunities and threats are described, and relate to the areas of key considerations associated with this part of a trial. Following this, Box 3 describes ICH-GCP considerations that are relevant to the Definition Phase of a clinical trial.

Table 12: Definition Risks

Internal Risks (11)

Study Design	Opportunities	-Restriction of trial entry (inclusion or exclusion criteria) protects subjects and controls the experimental setting - Use of a large population sample gives increased statistical power
	Threats	- Treatment period may be insufficient to produce clinical response - Over-restrictive inclusion or exclusion criteria make large scale subject recruitment impractical
Internal Processes	Opportunities	- Setting aggressive completion dates for critical path activities will allow early commencement of recruitment and accumulation of data
	Threats	- Unrealistic time constraints will cause disruption and increase likelihood of a trial failing to deliver as expected - Budgetary overspend increases risk to the trial, through insufficient resources to complete on time, and risk to sponsorship
Standard Operating Procedures (SOPs)	Opportunities	- Use of well established protocols allows ease of regulatory compliance, and planning of resources as appropriate.
	Threats	- Using SOP protocols that are new, and have not had the opportunity to be tested at length, increases the risk of inadequate quality of results, and GCP compliance

External Risks

Regulatory Authorities	Opportunities	- Designing the trial to comply with regulatory standards of the country and environment in which it will be run avoids delays to start-up.
	Threats	- Increased regulatory authority approval requirements that require protocol design changes before a trial can start
Market Potential	Opportunities	- Product fulfills an unmet clinical need (either through treating a previously untreatable disease, reduced adverse effects, improved administration etc)
	Threats	- Disease is already well controlled by existing treatments - Product has no cost, safety or efficacy advantages over competitors

Box 3: ICH-GCP Considerations during the Definition Phase

2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s). 2.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks. 2.3 The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society. 2.4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial. 2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol. 5.7 Allocation of Responsibilities. Prior to initiating a trial, the sponsor should define, establish, and allocate all trial- related duties and functions. 5.9 Financing. The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution. (37)
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Planning

Once the project has been defined, a detailed plan is made, together with the finalization of the protocol that will be acceptable to relevant regulatory authorities and ethics committees. A CRF (Case Report Form) is designed in order to capture all the trial data. Potential trial investigators are chosen, and it is ensured that they are adequately qualified to run the trial.

Submission to the IRB (institutional review board) for local ethics approval of a trial is the responsibility of the Chief Investigator. However, ethical approval can be lengthy, and failure of approval and answering queries can potentially slow down the progress of a trial. This is often a rate-determining step path to 'first-patient-in' and occasionally the preparation for this is often done by the sponsor CTU (clinical trials unit) should there be one involved.

As part of the planning process, adequate staffing levels are identified so that a qualified core team is available to run the trial, submission of the trial documentation to the regulatory authorities (ethics and local site approvals) also takes place. Investigator training and site initiation in preparation of the first trial participant inclusion also takes place in this phase.

The risks associated with the Planning phase of a trial are described below. Box 4 describes the ICH-GCP considerations associated with this phase of the trial. The Planning Phase risks focus on the set-up of the trial infrastructure and expertise in preparation for the first trial participant's inclusion – firstly, by ensuring that staffing and resources are adequate for participant recruitment, and secondly, through

ensuring regulatory bodies are aware of the trial, and all permissions and ethical approvals are in place. The ICH-GCP considerations are also related to these areas, and include the responsibilities of the investigator and the sponsors to ensure adequate resources to run the trial (resources include accommodation/offices, time allocation and adequately qualified team) and that there is support available in the form of a team of qualified individuals that can support the investigator throughout the trial process (the UK Medical Research Council (MRC) Guidelines for Good Clinical Practice (1998) (177) recommend that trial oversight should include an element of expert advice that is independent of the Chief Investigator (CI) and host institution involved) This oversight is usually provided by the Trial Steering Committee (TSC) (179). This group usually meets every 6 months, however, there are no guideline recommendations as to the minimum frequency of meetings (179, 180)

Table 13: Planning Risks

Internal Risks (11)

Investigator Suitability	Opportunities	- Using specialists in the target disease promotes both data quality and efficient subject enrolment
	Threats	- Selection of investigators who do not have access to appropriate patients causes enrolment and protocol compliance problems. - Selection of sites with inadequate facilities or qualified staff produces quality threats
Staffing	Opportunities	- Appropriate allocation of human resources to tasks results in completion of project to standards on time and on budget
	Threats	- Project may fail because not enough 'hands on deck' - Failure to adequately train all specialist team members results in less efficient working or quality problems

External Risks

Regulatory bodies	Opportunities	-An appropriate and targeted effort to secure support from sites that have established research experience and have worked collaboratively with other projects
	Threats	- Building a relationship and working with sites that do not have research experience – may require extra support with administration etc. - Ensuring allocation of service support costs and excess treatment costs
Site Set-Up	Opportunities	- Early discussion with site of IRB procedures and meeting dates allows timely ethics approval
	Threats	- Submission of inadequate or late documentation to IRB causes a deferral of decision to the next IRB meeting – site initiation is therefore delayed.

Box 4: ICH-GCP considerations during the Planning Phase

2.6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

2.7 The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

2.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

4.1 Investigator's Qualifications and Agreements

4.1.1 The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).

4.2 Adequate Resources

4.2.1 The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

4.2.2 The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.2.3 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4.2.4 The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

5.4 Trial Design

5.4.1 The sponsor should utilize qualified individuals (e.g. biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical trial reports. (37)

Implementation

Following the set-up of a trial, the inclusion of trial participants to the trial becomes the main focus of activity, adherence to the trial protocol is the aim of the trials team,

as patients are randomized to treatment, adverse events are reported, CRFs collected and data is monitored.

The risks described in the following tables largely focus around issues of safety of trial participants and ensuring that the trial goes to plan – ensuring that timelines are adhered to ensures that there is less risk of delays and associated budget implications. Consideration of participant safety, through ensuring all visits and follow-up points are chased up in a timely way, responsible data collection and maintenance of trial documentation is also essential in this phase of the trial. The ICH-GCP considerations describe adherence to trial protocol, maintenance of trial records and reports, and quality assurance to ensure responsible and adequate trial implementation and overall protection of trial participants at all times.

Table 14: Implementation Risks

Internal Risks (11)

Protocol Compliance	Opportunities	- Establishing project team work practices that follow the protocol with consideration of ICH GCP, ensures quality of clinical data from a study which can be shown to have been conducted in a statistical, ethical and legally acceptable manner.
	Threats	- Poor experimental design or protocol noncompliance may lead to a compromise of patient safety and welfare, and data integrity issues.
Safety and tolerability	Opportunities	- Safety of the drug under investigation can be further confirmed - Any side effects can be recorded as part of ongoing follow-up of the population
	Threats	- Unacceptable safety profile of treatment becomes evident during the trial or through subsequent analysis

External Risks

Eligible patient availability	Opportunities	- Establishing the population of individuals with a condition that are suitable for recruitment to a trial, a basis for planning future trials
	Threats	- Despite best efforts of site teams, an adequate number of eligible patients are not recruited – compromising the end result
Surveillance and laboratory issues	Opportunities	-Blood tests and profiles supporting a new treatment can be gathered. -A biochemical profile of a new disease population can be examined
	Threats	- Issues with laboratory samples, such as transport to lab, mislaid or lost samples. Risk of error increases if non-standard tests are taking place. Potential to compromise trial through inadequate data collection
Weather	Opportunities	-Planning participant interaction around safe ways of trial visits, through minimizing clinic or hospital attendance, gathering information in own home through nurse visits, telephone questionnaires etc.
	Threats	-Issues with transportation of lab samples, paper CRFs can mean unforeseen delays and deviation from protocol expectations -Poor weather can make a more frail patient population more reluctant to attend for review and research visits, again causing delays, increasing drop-out and issues with protocol compliance

Box 5: ICH-GCP considerations during the Implementation Phase

2.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

2.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

2.12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

4.5 Compliance with Protocol

4.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favourable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

4.9 Records and Reports

4.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

4.9.4 The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial, and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

5.1 Quality Assurance and Quality Control

5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

5.5 Trial Management, Data Handling, and Record Keeping

5.5.1 The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

5.15 Record Access

5.15.1 The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection. (37)

4.4 The Model of Organisational Accidents

4.4.1 Section overview

The basic idea of the model of organisational accidents is that human systems have multiple layers of defence so that, for a threat to become a reality, more than one layer has to fail. The corollary is that project failures have a systemic dimension which will not be uncovered by focusing on one layer of defence.

In this section, I describe the work of James Reason – based on the accident causation model, commonly known as the ‘Swiss Cheese Model’. It describes accidents, or adverse events in complex systems – and likens human systems to multiple layers of Swiss cheese, stacked side-by-side. The holes in the slices of cheese represent weaknesses in individual parts of the system, and are continually varying in size and position across the slices. The system produces failures, or accidents, when the hole in each slice aligns – forming a ‘trajectory of accident opportunity’ so that the hazard passes through all holes in defence, causing a failure (38, 181).

The concept of this model was designed as a normative way of demonstrating an organisation. Organisations – whether they have formed as a result of natural evolution, or through design, generally function in a hierarchical manner (181), and the majority of errors committed in real work environments are likely occur in a group, or team context (182). In this trial, a team of different individuals were working together in order to recruit patients and make the trial a success – the team

error taxonomy, proposed by Reason and Sasou, is described (39), and helps us to understand how the presence of co-performing team members affects the occurrence, detection and recovery of errors by any given individual.

4.4.2 Organisational layers, or the five productive elements

Accidents, or adverse events, such as in this case – the closure of the clinical trial – occur through the coming together of various factors in an organisation. Each of these factors as part of the complex system is extremely unlikely to cause the failure of the trial by itself, however, in rare combination, there is the possibility for the creation of a possible trajectory for an accident. Often these vulnerabilities are latent – and present in the organisation long before an accident occurs. These ‘latent factors’ can be a result of management decisions, or exist in the organisation as part of the organisational culture – allowing poor communication, hierarchical structure, and poor reporting of safety concerns (181). Preconditions or psychological precursors are latent states – they create the potential for a wide variety of unsafe acts (38) pp205.

All complex technologies are involved in some form of production, be it energy, services, chemical substances or passenger miles. All productive systems, it is argued, have five basic elements (183), these include, High level decision makers, Line management, Preconditions, Productive activities and Defences.

1. High-level decision makers: the “strategic apex”
2. Line management: departmental specialists of one kind or another (operations maintenance, training, etc).
3. Preconditions: a trained and motivated workforce together with appropriate technology and equipment.
4. Productive activities: the precise synchronisation of people and machines to deliver the right product at the right time.
5. Defences: various protective measures that are necessary when the system operates within potentially hazardous circumstances.

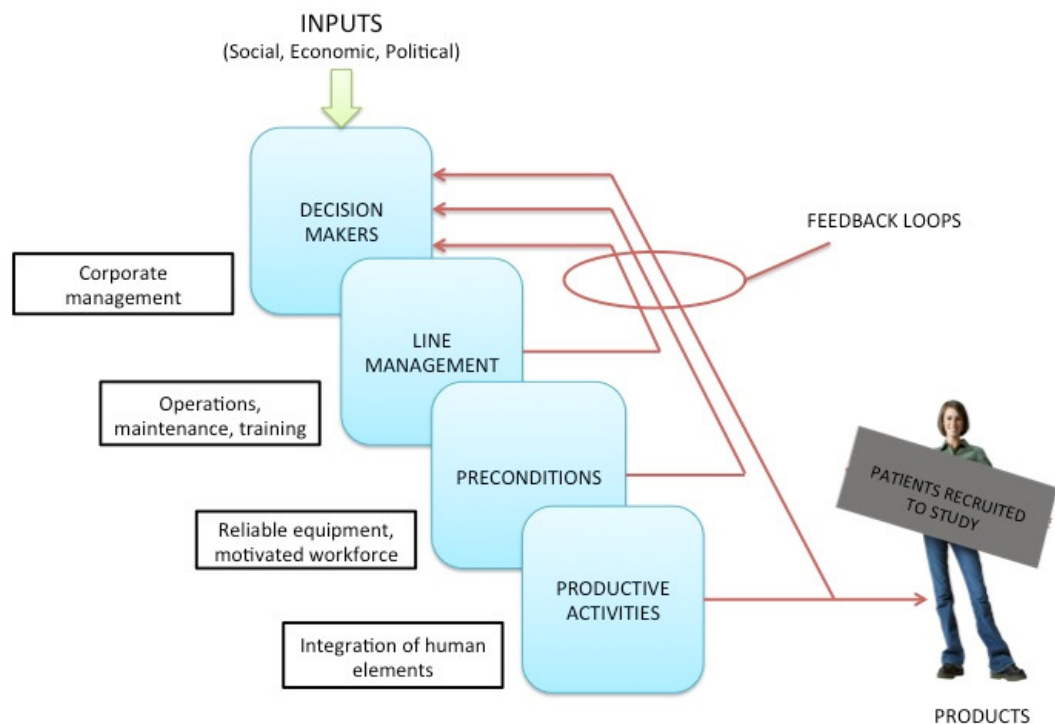


Figure 15: Five productive elements of all systems

4.4.3 Human contributions to adverse outcomes

Five human contributions to adverse outcomes, or accidents, are shown in the figure below:

Several causal factors are required to create a 'trajectory of opportunity' through these multiple defences. Active failures are unsafe acts (errors and violations) committed by those on the 'front line' of an organizational system. In healthcare for example, these may be doctors and nurses – members of an organization that are the

human-system interface, whose actions can potentially have immediate ramifications (138). Latent failures are created as a result of higher level decisions, often made at management and organisational level. These can remain dormant for a long time, combining with triggering factors in order to breach defences - Many of the causal contributions will come from latent failures in the organizational structure, or as a failure of the defences themselves (184).

An unsafe culture and organisational environment is more likely to be involved in the causation of organisational rather than individual accidents. It is the pervasive nature of culture that makes it uniquely suitable for creating and sustaining the linear gaps in defences through which an accident has to pass. Safety cultures evolve gradually in response to local conditions, characteristics of leadership, and the mood of the workforce (185).

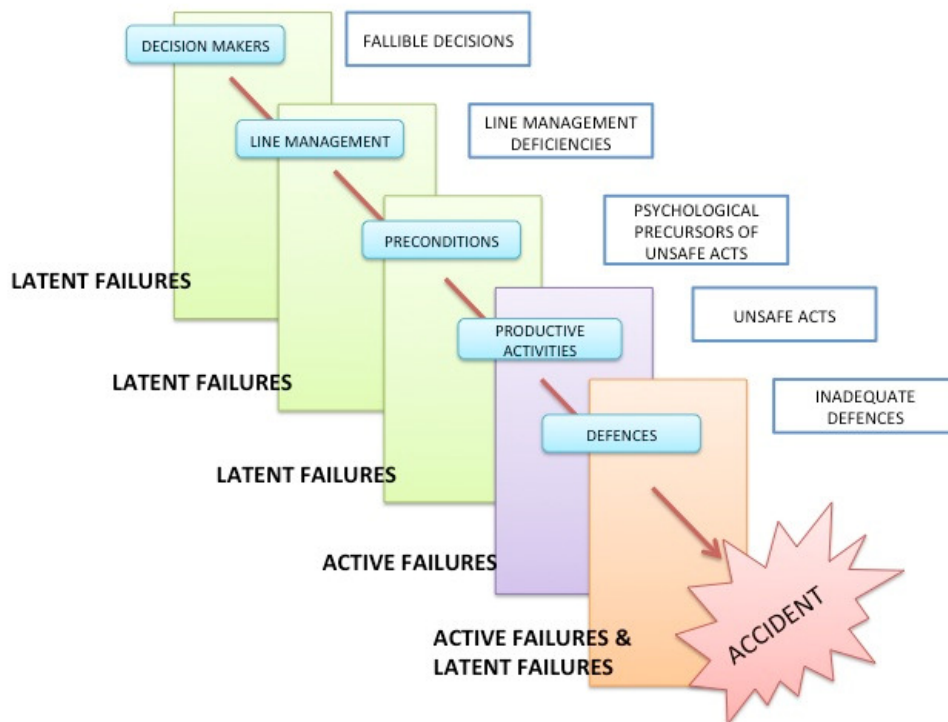


Figure 16: Five associated human contributions to adverse outcomes

4.4.4 Types and tokens: classes of failure

Types and tokens are both classes of human failure. They are distinguished in two ways: by their degree of specificity and by their points of reference within the organization. Types are general classes of organizational and managerial failures. Tokens are more specific failures relating to individuals at the human-system interface (186). **Source types** relate to fallible decisions at the strategic apex of the organization. **Function types** relate to the line management elements of any productive system.

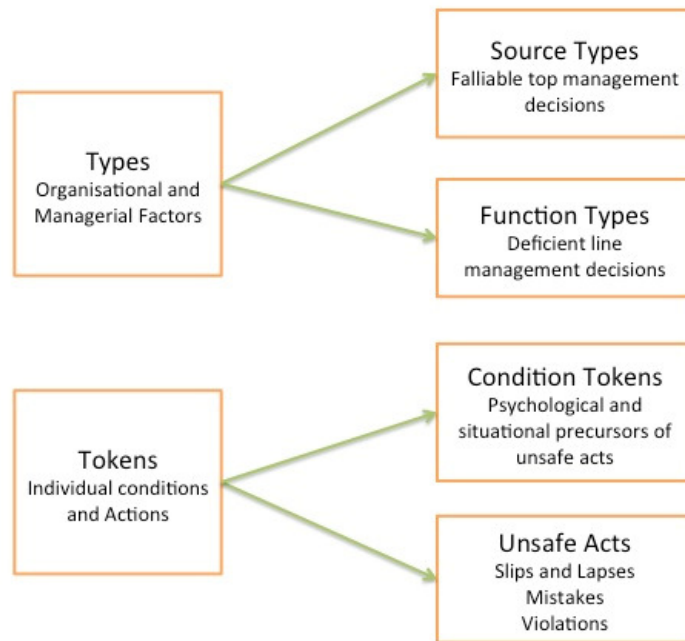


Figure 17: Types and Tokens

Psychological precursors are latent states. They create the potential for a wide variety of unsafe acts. The precise nature of these acts will be: a complex function of the task, the environmental influences and the presence of hazards. Each precursor can give rise to many unsafe acts, depending on the prevailing conditions.

There is a many-to-many mapping between line management deficiencies and these psychological precursors. Failures in the training department, for example, can translate into a variety of precursors: high workload, undue time pressure, inappropriate perception of hazards, ignorance of the system and motivational difficulties. Likewise, any one precondition (for example, undue time pressure) could

be the product of many line management deficiencies: poor scheduling, inadequate procedures, inappropriate training and maintenance failures.

A useful way of thinking about these transformations is as **failure types** converting into **failure tokens** (38).

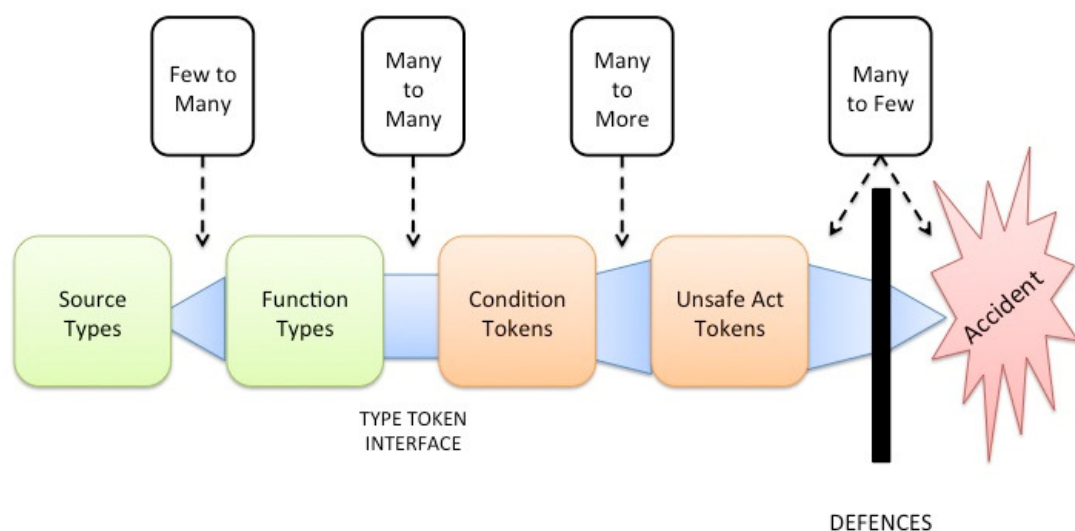


Figure 18 Relationship between Types and Tokens (186)

Deficient training is a general failure type that can reveal itself, at the precursor level, as a variety of problematic tokens. Viewing the relationship between types and tokens in this way has important implications when it comes to suggesting solutions, and preventing future accidents. The type-token distinction is a hierarchical one.

Precondition tokens at the precursor level (such as deficient training) become types tokens at unsafe act level (184).

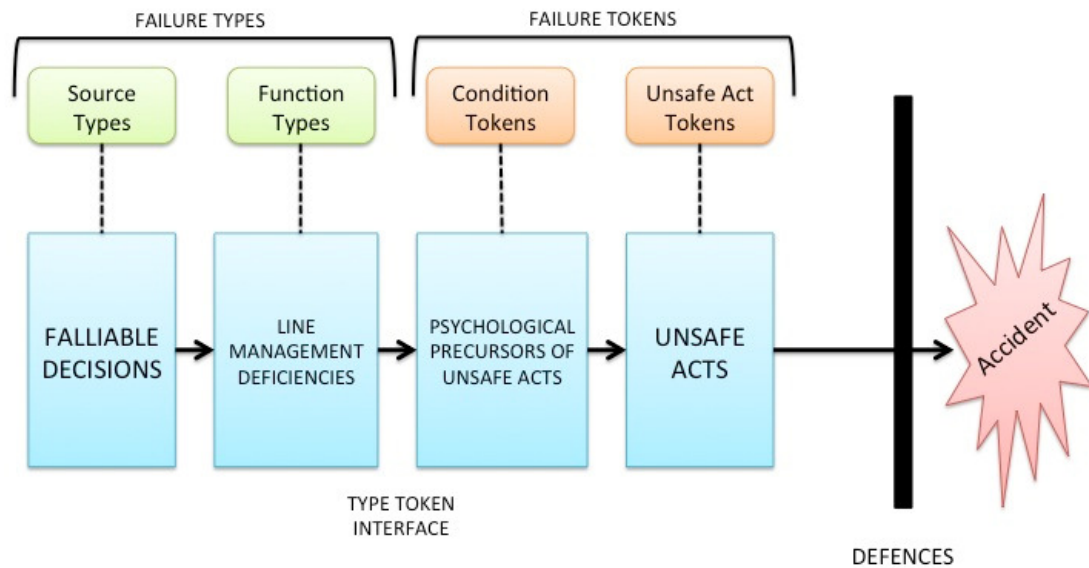


Figure 19 Dynamics of accident causation and indicators (38)

The diagram in Figure 19 shows a trajectory of accident opportunity penetrating several defensive systems. The indicators are divided into two groups: Failure Types (which relate to deficiencies in the managerial and organisational sectors) and Failure Tokens (relating to individual conditions and unsafe acts) – the diagram shows the relationship between Types and Tokens, and that of the model for accident causation.

4.4.5 Team errors taxonomy

Certain error factors that contribute to the culture of an organisation such that there is a higher likelihood of catastrophic error are discussed by Reason and Anderson here, in particular certain ‘team added’ factors, which included presumption of competence, and authority problems. For example, this pattern has contributed to a large number of aircraft accidents. A critical factor appears to be the unwillingness on the part of other crew members to challenge the authority of the captain (182) – seen in the case of this trial where there were members of the steering committee, and members within the sponsor organisations that felt unable to challenge the (187).

Sasou and Reason (39) discuss ‘Team Error’ – which considers how a group of people make ‘human errors’ whilst working in a team or group (38) – as demonstrated above, errors, or unsafe act tokens can be classified as mistakes, slips and lapses. As mistakes and lapses occur in the planning and thinking process – it is these two classes that are more likely to be associated with group processes (Slips occur in the action processes of a single individual, so are less likely to be associated with the activities of the team as a whole) (39)

The nature of decisions made in a group can often differ to that which an individual would make in the same situation. Groups will often make riskier decisions than an individual (188), and the influence of a power structure, so commonly seen in organisations such as healthcare and HEIs (189, 190), can affect how decisions are made – with the perception of group members being influenced more by high prestige figures, than their counterparts (191).

Two main areas need to be considered when assigning a classification to team errors, one is how an error occurs (the error-making process) and the other is how the error is not recovered (the error-recovery process).

Error-making process (39)

Individual errors are errors which are made by individuals. That is, an individual alone makes an error without the participation of any other team member. Individual errors may be further sub-divided into independent errors and dependent errors. Independent errors occur when all information available to the perpetrator is essentially correct. In dependent errors, however, some part of this information is inappropriate, absent or incorrect so that the person makes an error unsuitable for a certain situation.

Shared errors are errors which are shared by some or all of the team members, regardless of whether or not they were in direct communication. Like individual errors, shared errors may also be sub-divided into two categories: independent and dependent

Error-recovery process (39)

Failure to detect The first step in recovering errors is to detect their occurrence. If the remainder of the team do not notice errors, they will have no chance to correct them. Actions based on those errors will be executed.

Failure to indicate Once detected, the recovery of an error will depend upon whether team members bring it to the attention of the remainder. This is the second barrier to team error making. An error that is detected but not indicated will not necessarily be recovered and the actions based on those errors are likely to be executed.

Failure to correct The last barrier is the actual correction of errors. Even if the remainder of the team notices and indicates the errors, the people who made the errors may not change their minds. If they do not correct the errors, the actions based on those errors will go unchecked.

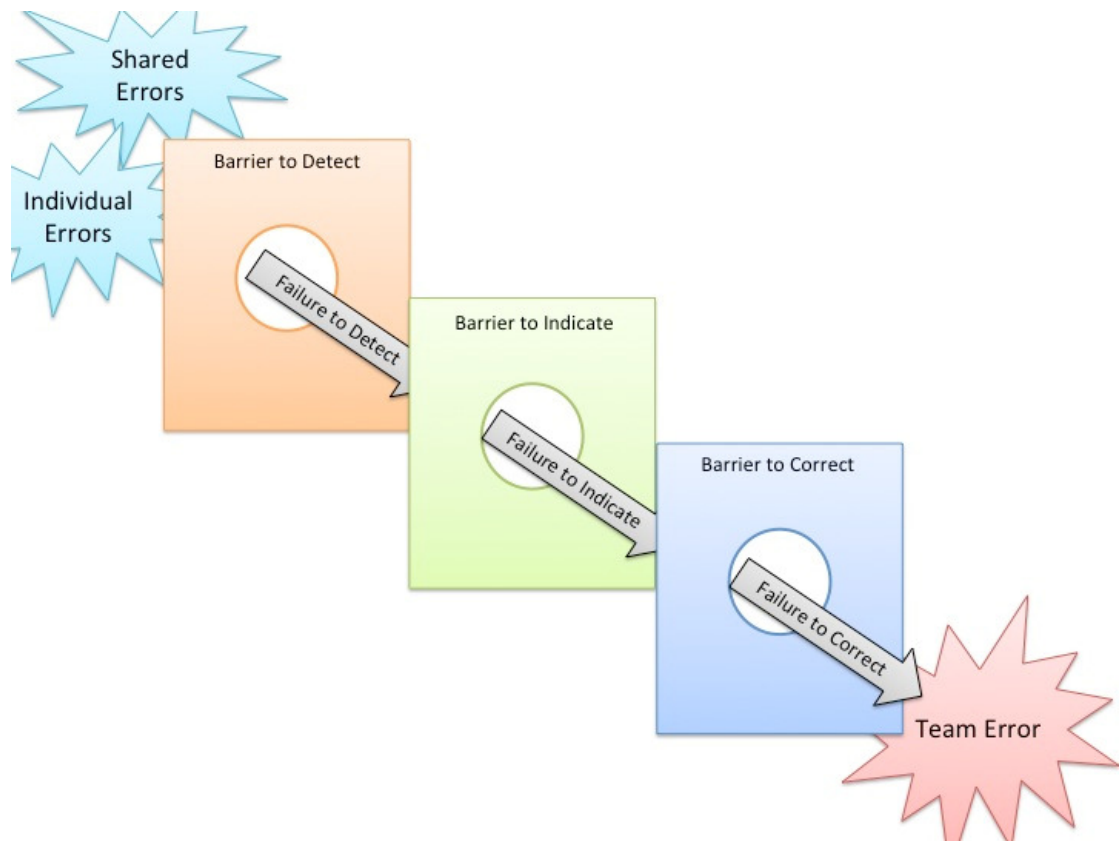


Figure 20 Team Error Process

The following associations are suggested by the authors (39, 182)

Shared errors are influenced by deficiencies in the human–machine interface, low task awareness, low situational awareness and excessive adherence/over-reliance.

Failures to detect are influenced by deficiencies in communication, resource/task management, excessive authority gradient and excessive belief.

Failures to indicate/correct are influenced by excessive authority gradient, excessive professional courtesy and deficiency in resource/task management.

The use of the Team Error model helps us to explore how the presence of co-performing team members affects the occurrence, detection and recovery of errors by any given individual (182). There is a relationship between perceptions of teamwork and status in the team (44). Attitudes towards hierarchy and teamwork is relevant to understanding error, and predictive in performance (35) – studies that have looked at

teamwork in an aviation context tell us that poor communication does not equate to an obstinate captain but to poor threat and error management at the team level (190), but that an excessive authority gradient in a team can influence how likely errors are indicated, or corrected.

4.5 Chapter Summary

Robinson's framework enables us to decompose a clinical trial into three phases – definition, planning and implementation. In any trial, the potential sources of failure at each stage are relatively standard but, while some represent generic 'project management' failures, breaches of ICH GCP principles are particularly important in the current regulatory context of clinical research. Robinson's framework and ICH-GCP principles provide a sound basis for the initial coding of qualitative data collected as part of my case study, abstracting from the specific to a more general level, but not yet explaining anything. James Reason's model of organizational accidents provides a sound basis for explaining 'how' and 'why' the trial failed. It posits that there are multiple layers of defence against failure in any organization and that large-scale systematic is necessarily a systemic matter. It classifies types of failure, so that one can understand why they occur and shows how they interact to produce undesirable outcomes. Reason's model has been well tested in other contexts; my application of Reason's model in the case study that follows (Chapter 7) will be the first in clinical trials project management setting.

5. Qualitative Methodology

5.1 Chapter overview

Thus far, as part of this thesis we have looked at the importance of clinical trials, and the role they play in providing robust evidence for treatment and management of health conditions. The literature has been examined, looking specifically at trials that have failed to recruit to target, and the common reasons for this. The overarching objective has been the examination of a specific clinical trial – using it as a case study in order to describe certain characteristics that may have contributed to issues that were encountered with recruitment.

In this chapter, research methodology is described, and includes an explanation of why certain methods and approaches were used. Clarification of theoretical stance is also included in this chapter.

5.2 Rationale, epistemology and research design

5.2.1 Rationale for using qualitative research

Qualitative methods are used to address research questions that require explanation or understanding of social phenomena and their contexts (192). The aims of research are directed at providing an in-depth and interpreted understanding of the social world, by learning about peoples social and material circumstances, their experiences, perspectives and histories (192). As this study is concerned with understanding and explaining what caused this case study trial to fail from the point of view of the professionals that were involved, qualitative methods are appropriate.

The relationship of the researcher and the participant is close in qualitative methodology, and this interaction can lead to an understanding of experience and generation of concepts (193). The data themselves have primacy, generate new theoretical ideas, help to modify existing theories or uncover the essence of phenomena. The theoretical framework of the research project is not predetermined, but based on the incoming data – although there may be some knowledge of the theories involved, or a ‘feel’ of what the potential outcomes may be, the incoming data might confirm, or contradict existing assumptions and theory.

I chose a qualitative approach to answer the research questions in this study for two reasons. First, qualitative approaches are better at exploring areas of human behaviours, beliefs, attitudes, and experiences, which cannot directly be answered or explored by quantitative approaches (194, 195). Unlike quantitative approaches such as surveys, using a qualitative approach takes an in-depth approach to the exploration of theories or topics, conveying an intensity and richness in detail to understand the topic of interest more thoroughly (196). A qualitative approach thus enabled me to gather rich and detailed data concerning the views and experiences of the employees that were involved in the trial.

Secondly, a qualitative approach has been used successfully in similar studies – such as Donovan et al 2014 (62) where qualitative methods were used to evaluate a series of in-depth interviews that were conducted with a range of primary recruiters at different stages of the implementation of a randomized controlled trial (RCT). A range of similar studies are described at length in the Literature Review (Chapter 2)

Qualitative methods, such as organisational ethnographies and case studies are best suited to address the complexities and multi-layered nature of healthcare, and similar organisations (197). Exploring and understanding issues such as professional practices and identities, and organisational structures and culture, and the broader societal beliefs and value systems require research methodologies that are able to analyse process and change, but also allow for diverse and possibly contradictory perspectives (198).

The use of qualitative methods is crucial for the understanding of organisational change, including the subtle and latent causes of organisational failure. In addition to those examples described as part of the literature review, in the wider literature there are examples of qualitative methods being used, such as Coulter et al (2008) examining the reasons why a centre for integrated medicine collapsed (199) and McDonald et al (2006) study into the ‘safety culture’ in an organisation (200). An alternative method to qualitative methodology would be to use quantitative methods in the form of a survey for example – as used by Scott et al (2000) (201) and Caronna et al (2010) in their multi-level case studies (197) showed how quantitative methods could help the investigators see the effects of organisational change, but qualitative uncovered complexities that quantitative methods would have overlooked. Similar points are made in Swanbourn (2010) (202).

5.2.2 Worldview or Epistemology

The worldview or epistemology underpins a researcher's choice of research strategy or methodology. A pragmatist worldview is orientated towards solving practical problems in the "real world" (203) rather than on assumptions about the nature of knowledge. It is therefore appropriate to the question of why the case study trial failed.

5.3 Research design, methodology or 'approach'

The clinical trial was used as a holistic single case study (204) with cross-sectional interviews. The holistic design is advantageous when no logical subunits can be identified or when the relevant theory underlying the case study is itself of a holistic nature (204). The label 'holistic' means that it is taken into account that the behaviour of people, and social phenomena are determined by a complex set of causes (202).

There are a number of ways of gathering data using a qualitative approach which were considered for this study. They include observation, document analysis, focus groups, and unstructured in-depth interviews (205).

Observation was impractical for this thesis because of the nature of the data required – the study involved approaching trial staff that had been disbanded following the trial closure. They had since moved on, either through a change in job role, or to other institutions and as participants in other projects. In addition, whilst observation provides richly detailed data, it is difficult to observe 'why' participants do what they do or feel how they feel (reasons for their attitudes or behaviours) (206)

Unstructured interviews were not practical in this study because I had specific and focused areas of enquiry - which semi-structured interviews were able to cover more efficiently (207). In addition, the data produced from unstructured interviews, whilst richly detailed is often non-comparable to other participants (196, 207), which is needed to achieve the objectives in this study.

Within the broad strategy of case study research, multiple methods are generally used in order to ensure a detailed investigation (208) This is often through participant observation, direct observation, ethnography, documentary analysis and interviews. In the pursuit of intricate interactions and processes within organisations, utilisation of a combination of methods in order to assess complex phenomena is recommended. In case study research utilization of multiple methods can in part improve validity of the findings through the ability of triangulating data and theory (209).

5.3.1 The use of semi structured interviews

Qualitative approaches are linked to the subjective nature of social reality, they provide insights from the perspective of participants, enabling researchers to see events as their informers do – also known as the ‘emic perspective’ in anthropological terms (210), where the researcher attempts to examine the experiences, feelings and perceptions of the people that they study rather than immediately imposing a framework of their own that might distort the ideas of the participants (193).

For semi structured interviews, a number of questions are prepared that between them cover the intended scope of the interview – these are prepared ahead and an interview guide is developed and supplied to participants as orientation. The questions are designed to initiate dialogue between the researcher/interviewer and the participant, but in contrast to questionnaires or more structured interview types, interviewers can deviate from the sequence and exact formulation of questions when asking them, and participants are encouraged to reply as freely and extensively as they wish. In this form of interview, should the answers not be rich enough, the interviewer can probe further. Open questions should allow room for the specific, personal views of participants, and avoid influencing them (193).

Semi structured interviews suited this study because it allowed the initiation of dialogue and improved the engagement and confidence of the participant through the provision of an interview guide, but also allowed the space and flexibility for the personal views of the participants to be explored and certain subjects and emerging themes to be probed and explored in greater depth (211), as the researcher can adjust the interview questions or use prompts to explore emergent themes as the interview proceeds (196, 207). Common prompts include “is there any other thing you would like to add” and “can you tell me more about that” (207, 212).

The limitation of focus group discussions is the area of maintaining confidentiality and anonymity within the group - participants might be hesitant in expressing their views (196, 205, 207). However, they can encourage participation from people who do not want to be interviewed on their own or feel that they have nothing to say (213,

214). Within the data-set that has been examined as part of this thesis, one focus-group interview was held.

5.3.2 The use of participant observation

The stance and the position of the researcher within a qualitative research exercise is extremely important. The researcher themselves is the main research tool (193), and their participation over an extended period in the field that is studied becomes an essential instrument of data collection (215). The immersion of the researcher in the setting and situation in the field is key in order to obtain a greater understanding of the context of participant's lives and the broader political and social framework of the culture in which it takes place (193). Koro-Ljunberg (2008) describes how participants have values and beliefs, and are also connected to their environment, and this influences their interactions with the researcher, for this reason – study participants should be seen as active collaborators and co-constructors of knowledge, rather than as objects of research (216). It is important to respect the culture and context within which a study takes place. If the researcher understands the context, they can locate the action and perceptions of individuals and grasp the meanings that they communicate (193).

Spradley (1980) describes the various degrees of involvement for a participant observer, from the bottom of the scale with an observer who has no involvement with the people or the activities studied 'Nonparticipation' – where data is collected through observation alone; through to 'Complete Participation' which constitutes the highest level of involvement, where the researcher studies the situation in which they

are already ordinary participants (217). Participant observation begins with wide focused 'Descriptive observations' for orientating to the study field, and to help to make research questions more concrete. Second, 'Focused observations' is more and more limited to the processes and problems that are particularly relevant to the research question, and finally 'Selective observation' at the end of the data collection finds evidence and examples to support these processes (217). The documentation for participant observation consists of detailed field notes and reflexive diary entries.

5.3.3 The use of documentary analysis

The use of existing materials, such as documents resulting from an institutional process, reports or diaries can also be used in qualitative research, and constitute data used for 'secondary analysis', in that this is data that was produced for other purposes (215) but is now being used for the analysis relating to this research question. Documents are classed as standardized artifacts, in so far as they typically occur in particular formats: as notes, case reports, contracts, drafts, death certificates, annual reports, letters, certificates or expert opinions (218). Several key documents relating to the case study trial may be found to be of relevance to the research question, and the study of the text may provide key insights into events that take place, and the timings of meetings and specific decisions; but in addition, exploring a text can often depend on what is said – and how an argument, idea or concept is developed – as well as focusing on what is not said – the silences, gaps or omissions. Different elements of text combine to consolidate meanings alongside assumptions in text (219). These approaches can be used to help to understand the organization of contemporary institutions.

5.3.4 The use of the Case Study approach

Case study approach was used as it allows the researcher to explore individuals or organizations, it also allows simple assessment through complex interventions, relationships, and communities. The case study is particularly suited to research questions which require detailed understanding of social or organizational processes because of the rich data collected in context.(220). This approach is especially useful where it is important to understand how the organizational and environmental context is having an impact on or influencing social processes (221).

Yin (204) suggests that a case study design should be considered when:

- (a) The focus of the study is to answer “how” and “why” questions;
- (b) Behaviour of those involved in the study cannot be manipulated;
- (c) Contextual conditions need to be covered because they are relevant to the phenomenon under study; or
- (d) The boundaries are not clear between the phenomenon and context.

All of which are relevant in the context of this case study analysis - This case cannot be considered without context – the environment in which the staff were working, it being a publically funded clinical trial, the culture of the department in which people were working and the influence of the sponsor organisations will have had an impact on decisions that were made, and potentially, whether any mistakes or errors took place, and how these then impacted on the failure of the trial.

A case study is expected to capture the complexity of a single case, and a case should be

- A complex functioning unit
- Be investigated in its natural context with a multitude of methods
- Be contemporary (204)

One of the advantages of this approach is the close collaboration between the researcher and the participant, while enabling participants to tell their stories (222). Through these stories the participants are able to describe their views of reality and this enables the researcher to better understand the participants' actions.

A case study has to be defined in terms of its theoretical orientation. This places emphasis on understanding processes alongside their (organizational and other) contexts. In some situations, grounded theory (223) may lead to emergent theory, while in other situations (such as this research) researchers may enter the case study organization with clear propositions to examine. The establishment of a theoretical framework is essential, as a case study may produce fascinating details about life in a particular organization but without any wider significance (209). The theoretical frameworks that were used for the analysis of the data are explained in chapter 4.

The use of a single case study for the purposes of this research has been documented in literature as being useful for the purposes of feasibility, but that the outcomes of using a single case study is not generalizable to the wider population (224), for example, whether the findings from this qualitative study into the failure of this

clinical trial can be applied to all clinical trials. However, a number of significant studies exist in the literature using a single case study, (such as the Cuban Missile Crisis (225), the Challenger space shuttle (226) and the operations within Glasgow gangs (227)) These examples have all looked at the subject matter within the case study through ‘drilling down’ to get as much intricate evidence as possible, and to examine the subject from many and varied angles to provide a rounded, richer, more balanced picture of the subject through using a range of qualitative approaches (228) – such as those described above.

Flyvbjerg (2001) describes the value of the single case study in how ‘getting close to reality’ on ‘little questions’ and ‘thick description’ can lead to answering ‘the basic concerns of life itself’ (229), which means that often small questions lead to big answers – taking the example of this study into this case of a clinical trial – it is a case study, there is only a single trial that is examined, although it cannot give a representative picture of all trials and the behaviour of individuals involved in clinical trials, the hope is that nevertheless there can be a rich understanding of the dynamics, tensions, pressures and motivations within clinical trials and similar organisations in general.

6. Methods

6.1 Chapter overview

In this chapter, the research strategy will be described. This chapter is organized in two sections, the first is that of a description of data collection. The next section describes the formation of the themes, and a description of the coding process. A description of initial approach to the data, using an inductive coding methods and elements of grounded theory is described. It is then described how a decision was made to revisit the literature, and to consider changing the approach. A deductive method of coding was then used, using a framework derived from the literature – the theoretical approach is described in Chapter 4.

The framework used for the analysis of the data obtained is based on existing theory that has been derived from the literature . A theory is a system of assumptions and principles posited to explain a set of phenomena (230)'. A framework is used to organize and manage data, and allows the researcher to analyse data by both case and theme (231). The theoretical approach (chapter 4) describes how themes were derived from the literature and based on theory, and this chapter describes how these themes were used in the framework for analysis.

A qualitative research methodology informed by ethnographic approaches was used for the study, the majority of the data was gathered through interviews with staff that were involved in the trial, available documents – such as the study protocol, and documents within the trial master file were also examined as part of this study.

6.2 Aims and Objectives

The aim of this study was to investigate the experiences and views of representatives from each stakeholder group that were involved at all stages of the case study trial, in order to develop a greater understanding as to why the trial failed.

6.3 Recruitment

6.3.1 Identification of participants

This study used purposive sampling to select potential interviewees. The potential participants for this study were those that represented the core stakeholder groups that were involved in the trial – across management and supervisory roles, and at the ‘front line’ of recruiting potential participants. They were all likely to be employees of HEI organisations, or employed within healthcare/NHS. Participants were selected and approached on the basis of typically being representative of the professionals that were involved in the trial, and represented each of the stakeholder groups.

I conducted the interviews myself, and had existing or previous professional relationships with half of the interviewees. Four of these were senior colleagues.

There are advantages and disadvantages with conducting research with colleagues or peers (232). The researcher may benefit from an understanding of the setting (233), and experience that helps to make the findings more meaningful (234). It is certainly likely that this sort of pre-existing relationship may have an impact on the

interviewer-interviewee dynamic, but it was ensured as far as possible that the questions from the interview guide were asked to all participants.

The nature of the setting, and my experience of working within the organization and previously being part of the core trials team meant that I had knowledge of potential participant's role in the trial, and so could use a purposive sampling approach to select a particular group representative of the group of interest – an approach that is justifiable when the research topic is one where the research question is in a specific area or around a particular topic (235, 236) In a study such as this, where the views and actions of the participants are the primary focus, it is common to use a sampling approach in which the selection of participants is based on their experience and knowledge of what is being explored. Purposive sampling allows the researcher to use their judgement to determine the suitability of potential participants, and this tends to be based on the participants' knowledge of the research topic (237).

6.3.2 Approach

Initially, I contacted participants via email, introducing myself and my role within the recently closed case study trial. The introductory email that I used is attached as an appendix (Appendix 2 pp313), and was reviewed and approved by my then supervisor, also the Chief Investigator of the trial. In order to improve confidence and ensure that participants were aware that the review of the case study trial performance was taking place with the full support and awareness of the chief investigator, he was copied into each email.

6.3.3 Relationship with participants

One of the challenges with this study was that of engaging with individual members of the trial stakeholder groups – there were a number of factors that may have played a part in their readiness to engage with the process – These included

- Time pressures of other work projects
- The perception that participation in a project such as this may uncover sensitive information that may adversely affect their colleagues and damage professional reputations

The first wave of recruitment and the associated interviews were limited, and initially many potential participants initially refused. However, once the first few participants were interviewed, uptake did improve when colleagues had discussed it amongst themselves – some participants approached me after initially refusing to have any involvement at all.

6.3.4 Participant knowledge of the interviewer

Through my involvement in the case study trial as clinical researcher, I already had a degree of rapport with a number of individuals that were involved in the trial – particularly those working as part of the local project team, and within the sponsor organisations. I had met a number of members of the trial steering committee and co-applicant group through investigators meetings, and through my involvement in local clinical research projects.

The establishment of rapport was essential in this case – particularly as a way of establishing a safe environment where the interviewee feels comfortable enough to

share their personal experiences and assured as to the respect and confidentiality that their contribution will be given (238). Palmer (1928) suggests that when investigators are examining groups of which they themselves are members, it is possible to secure intimate, confidential type of material that is only through the type of rapport that is built up gradually, through the sharing of experiences (239).

Interview participants were aware of the study, and knew that I was a post-graduate student seeking to look into the reasons why the trial failed to progress. They were made aware of my role within the trial and that I was pursuing a doctorate and (at the time) was under the supervision of the Chief Investigator. Conducting qualitative research and interviewing peers has advantages and disadvantages – familiarity with the environment and situations that interviewees are describing is an advantage, and establishing a rapport and trust with the interviewee may confer an openness to any exchange (240).

6.3.5 Interviewer characteristics

Given my background and role within the case study trial, and my familiarity with the majority of the interview participants - my reasons for conducting the research, and my role in the closed down trial was declared to all interview participants prior to the interview taking place.

6.4 Sampling strategy

6.4.1 Description of the sample

A stakeholder diagram that illustrates the groups and organisations that were involved in the case study trial is illustrated below.

Sampling strategy involved :

- Identification of organisations and groups that were involved in the trial
- Identification of individuals that had key roles in these stakeholder groups and had direct involvement with the trial

I have included a further diagram that shows the stakeholder groups and their interests and motivations with being involved in the trial (Figure 21/22).

The indication of the role and action arena of each stakeholder indicates the relative priority given to meeting the interests of each stakeholder, and therefore assessing the importance of each stakeholder to the success of any project (241). An inventory of the key players involved, and the institutional motivations and roles within a project are essential information in order to get an overview of the organizational structures involved, and to identify each one's role in the trial structure(242).

Figure 21 Trial Stakeholders

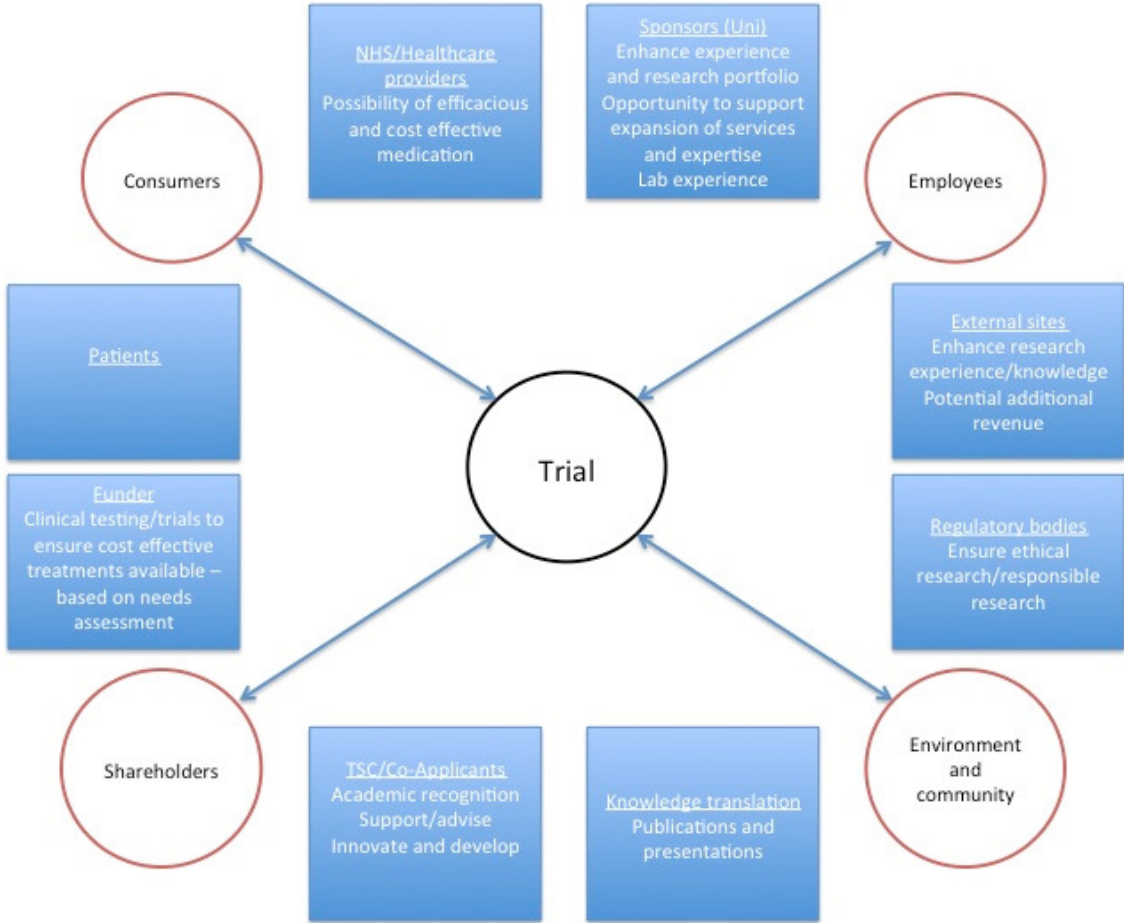
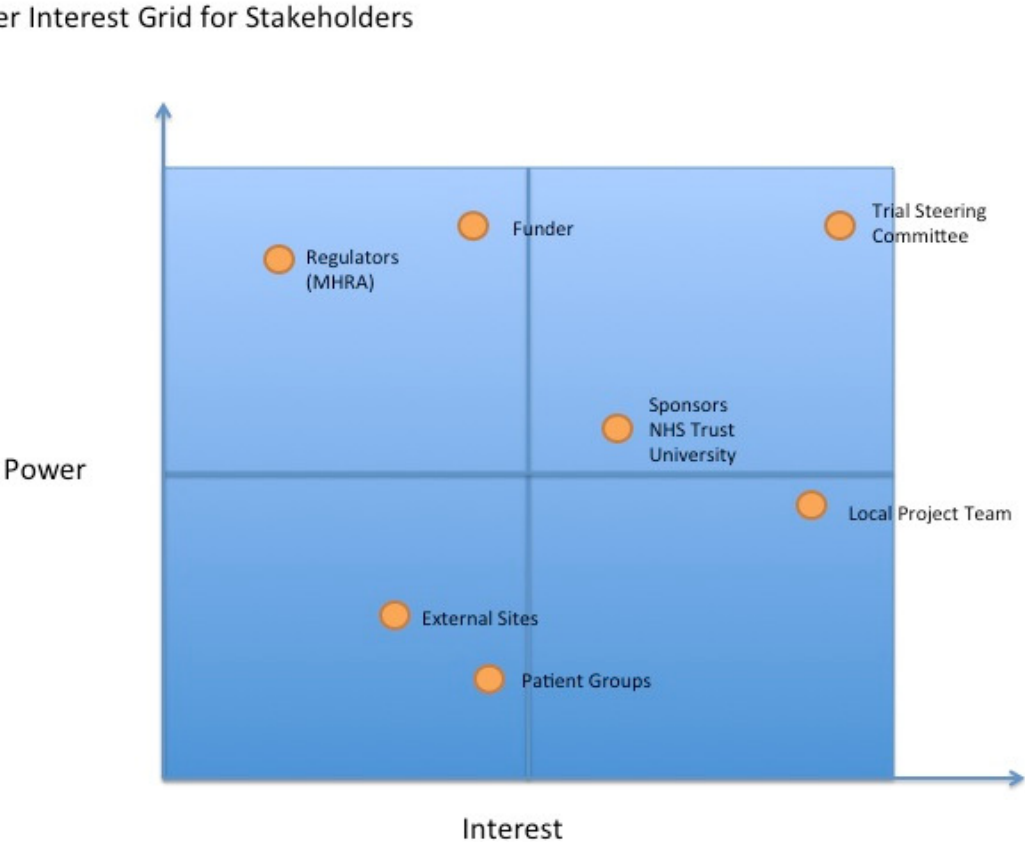


Figure 22 Stakeholder Position/Interest



Stakeholder groups were selected on the basis of their involvement in the trial.

Table 15. Interview participants on basis of stakeholder group

Stakeholder group	Participant
Funding body - A	A1
Sponsor (NHS Trust) - B	B1 B2
Sponsor (University) - C	C1 C2 C3
Trial Steering Committee - D	D1 D2 D3 D4 D5
Local Project Team - E	E1 E2 E3
Clinical Trials Unit (CTU) - F	F1 F2
Co-Applicants - G	G1 G2
University Department - H	H1 H2
Research teams at external sites - I	I1/I2 – Focus Group

6.4.2 Sample Size

Qualitative research unlike some quantitative methods has no strict rules as to the correct sample because one is not making inferences about estimates (207). Some researchers have suggested different sample sizes for different qualitative approaches: Morse (1994) (244) suggested: 30 -50 interviews for an ethnographic approach, 30-50 for grounded theory approach and at least a sample size of 5 for a phenomenological approach. Creswell (245) suggested 20-30 interviews for grounded theory approach and 5-25 for phenomenology approach. Guest and his colleagues (2006) (246) suggested that 15 is the smallest sample size acceptable for all forms of qualitative research. Others suggest following the approach known as saturation, which according to Ritchie et al. (2013) (192) is the point of diminishing return to the qualitative sample when an increase in sample size does not necessarily lead to more information.

Having established that there are no clear-cut rules to appropriate sample size, Baker and Edwards (2012) (249) suggest that the decisions about sample size should be made with a number of considerations: the resources available, the time frame of the study, and whether the sample is large enough to reflect the variation within the target population.

22 interviews took place in order to gather the data.. The first interviews conducted during the pilot phase, during which time questions were revised, included one focus group.

There were a total of 21 ‘one to one’ interviews, with 21 different individuals representing all stakeholder groups. In addition to this, there was one focus group interview. This took place with 2 individuals with a research team recruiting at an external site. The data was used for the analysis as it contributed a valuable insight from one of the few external-recruiting centres. All the data obtained from these 22 interviews was transcribed and subsequently used for analysis. The total number of participants was 23.

6.4.3 Non-participation

In addition to the 22 interviews described above, there was one interview that took place with a member of the ‘Co-Applicants’ group that was terminated early at the request of the interviewee. They also declined for their audio recording to be utilized, they did however provide a 600 word written statement addressing each point on the list of planned interview questions, and provided their consent to the utilization of the statement for subsequent analysis and for the purposes of this research. This statement was utilized as additional data (along with other key trial documents), and used in the analysis.

6.5 Setting

6.5.1 Setting of data collection

Interviews took place in participant’s own place of work, either face-to-face, or if the participant preferred, over the telephone.

6.5.2 Presence of non-participants

No other people were present during interviews apart from the participant and researcher/interviewer.

6.6 Data collection

Data was collected from February to December 2014 (one year after the official closure of the case study trial, and 6 months after the ‘last patient, last visit’ point)

A key summary statement was used at the start of each interview, with the aim of ‘scene setting’. A series of five open ended questions were then used in order to stimulate discussion if needed. A copy of the summary statement and questions is attached as an appendix (Appendix 3).

6.6.1 Interview guide - developing interview questions

According to Merriam et al (251), the key to obtaining rich reliable data from interviews is by asking ‘good’ questions that reflect the research question(s), which are often informed by preliminary observation of the context and relevant literature. Good interview questions according to Creswell (245), should be well-informed, non-leading, and unambiguous. The following paragraphs describe the process and features of the interview questions and how they were developed to ensure the credibility of this study.

6.6.2 Piloting of the interview guide

Firstly, I conducted preliminary informal talks with members of academic staff that were involved in the case study trial – predominantly heads of those departments that raised concerns about the closure of the trial. Through these talks we identified the importance of examining the study, and the reasons why it may have failed to progress in the way the trial organisers had hoped.

The closure of the trial was at a time when there was concern about the difficulty and mounting complexity associated with running a clinical trial. There had been a recent downturn in research and associated investment over the preceding few years - In 2002, 46% of EU products in clinical trials were being developed in the UK; by 2007 this had fallen to 24%. (252) Between 2000 and 2006, the proportion of patients recruited from the UK to the world's commercial clinical trials fell from 6% to 2% (253). It was thought that this trial could be an effective case study in demonstrating the difficulties in pursuing clinical research within the NHS.

Due to the catastrophic nature of the collapse of the study – I looked to the local NHS department of risk management within the NHS trust, in order to see how they investigate events – in particular the evaluation of system failures and ‘never events’ within healthcare. ‘Never events’ are serious, largely preventable patient safety incidents that should not occur if adequate preventative measures have been implemented (254) – examples of such events include wrong site surgery, or retained foreign object post-procedure.

During my time spent with the risk management department, I was told about the range of tools that were used to assess untoward incidents that occurred in healthcare. The most common approach used within NHS trusts (255) was to undertake a ‘Root cause analysis’ – this is a process for identifying causal factors that underlie an adverse event, with the view that the identification and correction of system issues may decrease the chance of recurrence of an undesirable outcome (256). The most appropriate tool was for the assessment of ‘Never events’ (27) and was based on the ‘5 Whys’ (257) – a tool developed in the Toyota Production System in the 1950s, and I will explore this in more detail later in the chapter.

The areas of importance that I set out to explore through discussion with people that were involved in the case study trial were –

- The reasons why they felt that the trial failed to progress in the manner that the project team had hoped
- Whether they felt that anything could have been done to prevent the outcome
- Their understanding of how they felt that the trial was progressing
- Whether there were things that they learnt from being involved in the trial
- Whether their experience would affect future project involvement, or inform their future choices.

I then developed questions around each topic – the aim was to ensure that the question structure was open, and designed in a non-leading manner, this was to increase the credibility of the study by ensuring that as far as possible that my own opinions about the subject matter being discussed was not expressed (251).

It is important to note that there is, throughout this research, the risk of bias. Marshall and Rossman (258) advise it is important to note - in the field of applied sciences there is often a strong autobiographical element that drives the research interest. Although one of the main challenges of the qualitative researcher is to demonstrate that this personal interest will not bias the study, if direct experience stimulates the initial curiosity (as my experience as clinical researcher within the department, directly involved with the case study trial did) that the researcher needs to link that curiosity to general research questions (as in this case) and acknowledge their position through the stages of analysis.

I made sure the questions were not ambiguous by having just one idea per question and using simple language, which helps participants understand the questions, thereby producing more reliable and credible data (194).

The questions were designed around the 'Five Whys' concept – a simple technique adapted from the Toyota Production System (257), and now commonly used in healthcare in the UK in order to determine the root cause of a problem (30). This technique involves repeatedly asking 'Why?' until the root cause is identified, which on average requires five iterations. The main drawback to this technique is that it can be quite annoying for the interviewee, so it is highly recommended that structured questions are used in the query (30) examples include :

- The trial closed prematurely – Why do you think that was?
- Do you feel that there were particular factors that may have played a part in why the trial was closed early and the funding was withdrawn?

- Why do you think that ...(particular situation/causative factor)... occurred?
- You mentioned earlier that ...(particular situation/causative factor)... was an important reason as to why the trial closed, could you tell me more about why you think this happened?

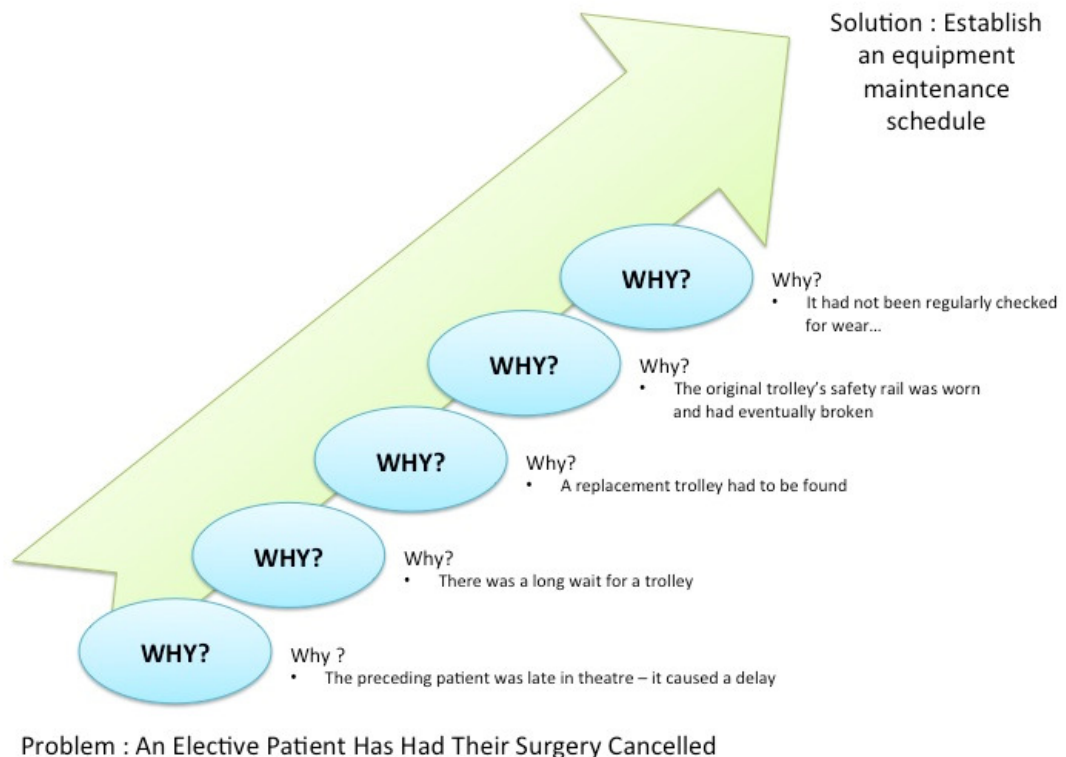


Figure 23 An example of the ‘5 Whys’

Following the development of an initial schedule of questions – I piloted them on two staff members that worked with the central trials management team on behalf of the hospital trust - sponsors of the trial, and with a small focus group based in one of the external trials sites. This helped to improve my interview skills, and gave me the opportunity to review the questions and refine them as necessary.

I reviewed these initial transcripts with my co-supervisor at the time. We took the opportunity to look for emergent themes (ideas/themes that emerge from reviewing the data) in order to inform further questions, and to choose other potential interviewees to approach from the various stakeholder groups.

Table 16 Preliminary interview questions – pilot

Areas of interest	Related questions
The reasons why the interviewees felt that the trial failed to progress in the manner that the project team had hoped	The trial closed prematurely – why do you think that was? Which factors in particular do you feel were important? Why do you think that ... occurred?
Whether they felt that anything could have been done to prevent the outcome	Do you feel that there were factors that if changed, might have changed the outcome, and perhaps prevented the trial closure?
The interviewee's understanding of how they felt that the trial was progressing	Could you tell me about your experience? How did you feel the trial was going?
Whether there were lessons to be learnt from being involved in the trial	Do you feel that there might be lessons that you personally might have taken away from your experience with the trial?
Whether their experience would affect future project involvement, or inform their future choices.	Will your experience and involvement in the trial influence your future research practice?

Conducting these pilot interviews helped me to develop an understanding of what questions worked and elicited rich answers, and which worked less well. It also helped me become more fluent, as there were a number of interviews that had to be conducted over the phone, because of interviewee's time constraints and availability. It also helped me to make a few changes to the interview schedule, with the aim of improving the experience for the interviewee – an important step in order to ensure

they felt more comfortable, and able to give honest answers (259). The changes were as follows:

In addition to the email/letter of introduction and description of the aims of the study supplied to all participants at the time of interview, a brief description of the main questions to be asked were also supplied. This was following feedback from one of the pilot interviews, the perceived sensitive nature of the topics for discussion meant that there was some anxiety on the part of the interviewee prior to the interview. He did feel that more detailed information in the way of the questions and their open nature would have helped to allay that anxiety.

Review of methods – the focus group was useful, it did engage more participants and encouraged those that did not feel they had much to contribute to participate in the interviewing process – however, it was a less practical method as the majority of the potential interview participants were based in different parts of the country, and did not add very much extra information – it was decided therefore to pursue one to one interviews.

I reframed some of the prompts – in particular around the ‘Five Whys’ questioning – simply asking the same question over again in a different way did make interviewees impatient, and may have affected how closely they felt I was listening to their responses. I had available to me a list of semi-structured prompts that I could use, and reflected back previous responses in order to encourage deeper discussion as to the root causes of the trial failure.

I also added onto my ‘setting the scene’ preamble – the aim of which was to put the interview participant at ease, to explain the purpose of the study and to thank them for their contribution – that ‘I would be asking a number of questions about their experience and involvement with the case study trial, and that at times during our discussion it may seem that I am repeating myself, or asking the same questions, but that the purpose of this is to gain a deeper understanding of the underlying causes for the failure of the trial to progress as everyone had hoped.’

Finally, piloting the interview schedule gave me the opportunity to practice being comfortable with long silences and slow movement between areas of interest – discussion with my co-supervisor helped us to use techniques used in clinical work to aid interviewing.

6.6.3 Interview Sessions

Data collection took place over several months – the first interviews taking place in January 2014, and the final one in November 2014. Interviews took place with individuals in no specific order, and as far as possible interviews took place on a face-to-face basis in a private place chosen by the interviewee – usually their office at their place of work. In those situations where it was not possible to meet, interviews took place over the telephone. Choosing familiar surroundings for the interviewee is thought to aid a relaxed environment, thereby resulting in productive interview (260).

The interviews began with my reading out a ‘scene setting’ statement, a copy of which, and the basic questions that we planned to cover over the interview, were

provided to the interviewee beforehand. I also took the opportunity at this point to assure the interviewee that their contribution would be confidential.

The first questions that I asked the participants were general, asking about their experience and role within the study. We then, once the interviewee was happy to proceed, commenced with the more formal scene-setting statement, and then the interview questions. During the interview I also used both affirmative words and body language to encourage openness and further conversation, I also reflected back statements made by the interviewee (using them as probes) in order to explore certain subjects on a deeper basis.

6.6.4 Repeat interviews

No repeat interviews took place.

6.6.5 Audio/Visual recording

The interview sessions were audio recorded, with the permission of the interviewees. These were using a digital voice recorder, downloaded onto an encrypted memory stick and stored on a hospital issue computer suitable for storage and manipulation of patient specific data.

6.6.6 Field notes

I also listened carefully, took notes and impressions of participants during and after the interviews. This then was integrated into later analysis and formed part of the raw data set.

6.6.7 Duration

I ended each interview by thanking the participant for their time and contribution. Each interview lasted an average of 30 minutes. The shortest being 16 minutes, and the longest 90 minutes.

6.6.8 Data saturation

Failure to reach data saturation (246) has an impact on the quality of research conducted and can affect the validity of the results (261). Data saturation is reached when there is enough information to replicate the study, when no additional new information is attained (no new data), and no new subjects or themes are evident despite analysis of additional raw data (no further coding).

However, there is no 'one size fits all' method to reach data saturation, and dependent on study design, and the question being answered. Landau and Drori used an inductive grounded theory case study analysis in a research study centred in an R&D laboratory, in this case a cross-section of the organization's employees were interviewed, in order to determine viewpoints within the workplace. Data triangulation was used in this case in order to enhance credibility (262) – this is discussed in more detail towards the end of this chapter.

In this case study, data from all the interviews were collected and analysed first inductively, with no new themes arising after the 16th of 22 interviews (an example of data saturation) (263); when applying existing frameworks deductively, a good fit was identified between the data sets and the frameworks.

6.6.9 Transcripts returned

Transcripts were reviewed by researchers, and all participants were invited to be sent a copy of the complete transcript at the end of the interview, however all declined.

6.7 Data Analysis

In order to complete the analysis of data generated from the semi-structured interview, I used the framework method. The Framework Method was developed by researchers, Jane Ritchie and Liz Spencer, from the Qualitative Research Unit at the National Centre for Social Research (NatCen) in the late 1980s for use in large-scale policy research (231). I also attended a two day course at NatCen, in order to learn methods of qualitative analysis and specifically how to use the framework approach.

Framework Method was appropriate for this study for a number of reasons.

First, the matrix output proves an efficient way to organise, manage, and become familiar with the data, which is practical and feasible in this study to explore the variation in the views and experiences of the individuals interviewed across the various stakeholder groups (264, 265)

Second, Framework is adaptable for both pre-set themes (deductive approaches), and emergent themes (inductive approaches) (266), which was appropriate for this study in which emergent themes were anticipated

Third, the stages by which the results have been obtained from the data are clear, visible and systematic, (264)

Fourth, Framework significantly facilitates comparison of data across the matrix (264), which was important in exploring and comparing the variations in views and experiences across the groups and individuals that were interviewed

The framework approach consists of five stages: Familiarization with data, Identification of thematic framework, Indexing/coding, Charting, and Mapping and interpretation (231).

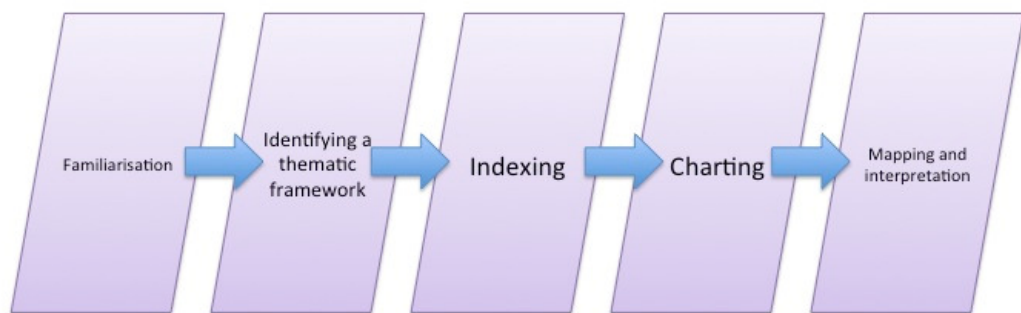


Figure 24 Stages of the Framework Method

6.7.1 Familiarisation with the data

Familiarisation of the data involved transcription, using contextual and reflective notes made at the time of interview, and a preliminary interpretation of the text in

order to facilitate coding. For Framework, it is not necessarily important to include the conventions of dialogue transcriptions which can be difficult to read (e.g. pauses), because the content is what is of primary interest (36).

After initial transcription, I further thoroughly read each transcript several times, making notes and writing down impressions of possible emergent themes as I went through the dataset. I also took my initial transcribed interviews and worked through them in order to look for themes with my co-supervisor. Each transcript was stored on an encrypted password protected memory stick. One way to increase the validity, strength, and interpretive potential of a study, to decrease investigator biases and provide multiple perspectives is to use investigator triangulation (267, 268)– as described above.

6.7.2 Identification of the thematic framework

The second step taken in the analysis was to develop the thematic framework, which involved identifying and refining initial and emergent themes. Initially I derived a coding framework inductively, but was unable to structure the codes into a coherent whole. At this point I performed a number of literature searches for social science theories which had bearing on the themes which were arising, especially those related to project management and cognitive science studies on biases and heuristics. After trying a number of different theories and frameworks, I settled on using the frameworks and models described in Chapter 4: ICH-GCP; Robinson's framework for understanding clinical trial risk management and, Reason's model of organizational accidents.

6.7.3 Indexing / coding

The thematic frameworks identified in Chapter 4 were systematically applied to the data in its textual form. I used NVivo version 11 (QSR International, Warrington, UK) to index transcripts with codes related to ICH-GCP, and the models described by Robinson and Reason.

6.7.4 Charting

Charting involved grouping themes and subthemes, elaboration of themes, and comparisons of themes across the participants. After coding of the data, I entered the summarised data into a framework matrix in order to easily look across the dataset to identify patterns and connections within and between the themes. These tables are presented throughout the results section, below. Good charting requires an ability to strike a balance between reducing the data on the one hand and retaining the original meanings and ‘feel’ of the interviewees’ words on the other. The chart should include references to interesting or illustrative quotations (36).

6.7.5 Data interpretation/Mapping

Mapping and interpretation involves searching for patterns, associations within the data, and linking the interpretation of the themes to construct an explanation or meaning. If the data are rich enough, the findings generated through this process can go beyond description of particular cases to identifying areas that are not functioning well within an organisation or system (36). A diagram summarising my findings is presented in the results section below.

6.7.6 Description of the coding tree

An example of the coding tree is described in an appendix 4 (pp314)

Indexing/coding involved applying the thematic frame work to the data using labels or codes that correspond to different themes. Initially, I reread the transcripts several times to develop, inductively, textual codes or categories, which summarised views of the interviewees within each theme while retaining links to original data. After these proved difficult to summarise, I introduced an explicit social science theory element to the analysis.

The diagram in Figure 4 describes the 3 themes for analysis of raw interview data. These are defined as the three phases of a clinical trial, and the relevant ICH-GCP considerations. This was the thematic framework that was used to index and chart the data, using qualitative data analysis software.

Using this framework to chart the data will help to identify the areas and events that led to the failure of the trial – Using the work of James Reason will then help to map the results and to identify the error types, including those that are skills based (slips and lapses) and those that are knowledge or rule based (mistakes) (38) pp95. This will help to differentiate the type of activity that was going on, and to better understand the focus of attention, and the influence of situational factors on the trial failure.

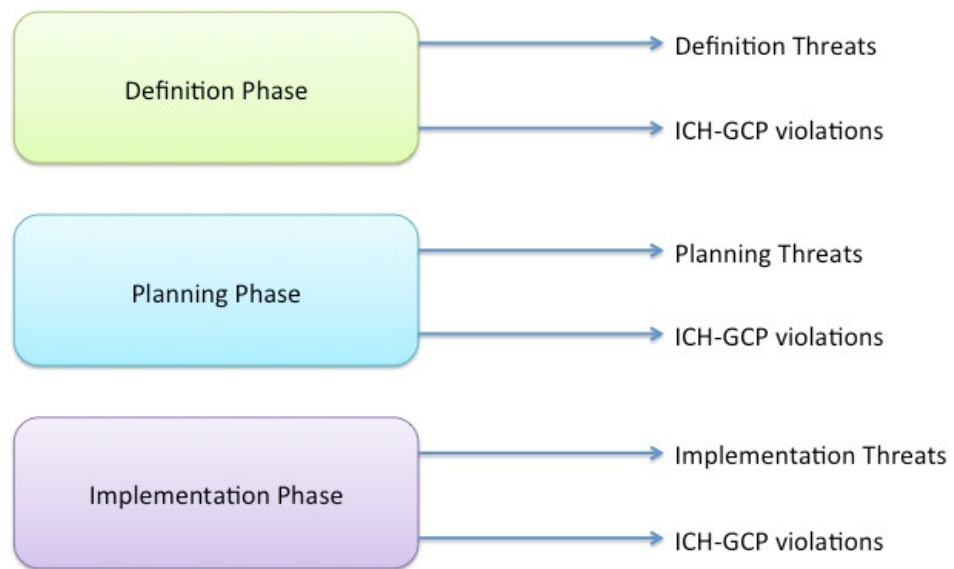


Figure 25 Coding tree

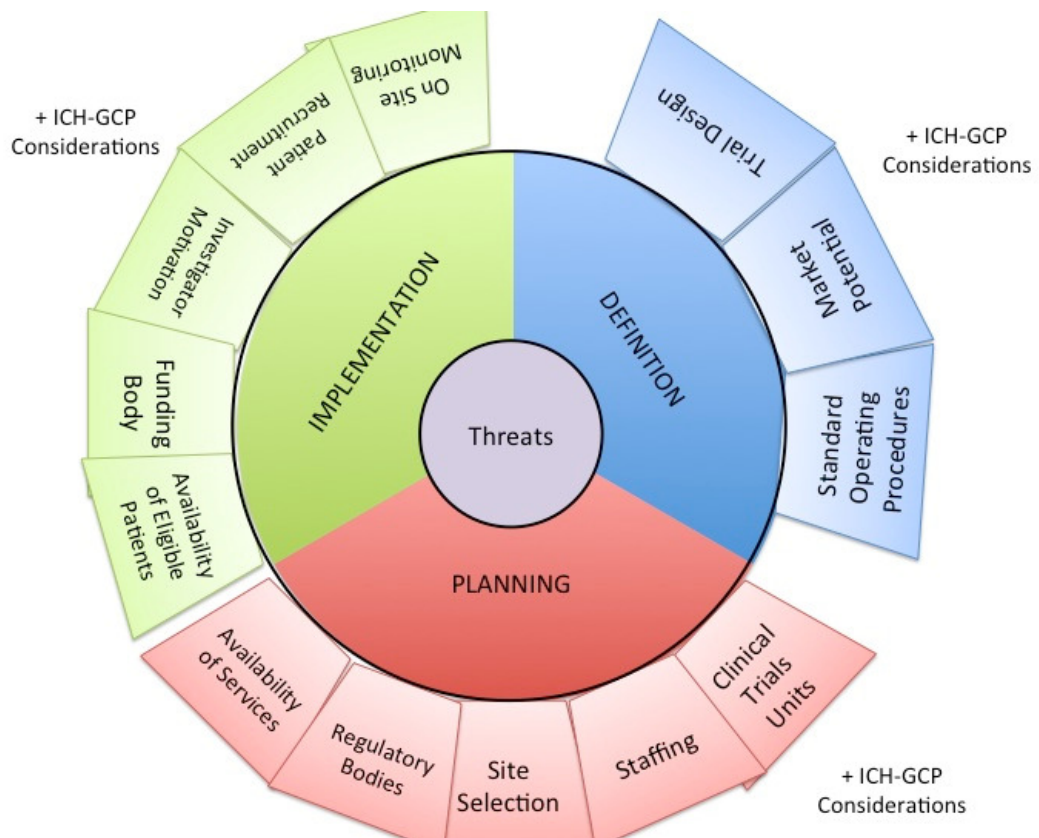


Figure 26 Description of the final coding themes

6.7.7 Participant checking

Participant checking did not take place, and participants did not provide feedback on the findings.

6.8 Strategies to improve the trustworthiness of qualitative work

In contrast to quantitative research traditions, which view objectivity as a goal, qualitative researchers recognize that by the very nature of the data that is gathered, and the manner in which it is analysed means that the research process is grounded in subjectivity (269). A statement of my experience and the manner in which I was engaged in the trial, and therefore the research situation that is under examination is

described in the introduction – this sort of engagement in the research situation can ensure an in-depth understanding of the phenomenon under investigation, and an extra and unique viewpoint to add to the analysis (270).

6.8.1 Adequacy of Data

The sheer number of interviews or a tally of the number of documents analysed cannot assure the quality of the findings in this kind of research (271). There are various numbers that are often recommended in the literature, and these vary greatly, with Merriam describing that ‘quite a lot’ can be learnt from a sample size of 1 (269, 272), and others describing numbers that are much larger. Patton (273, 274) describes that validity, meaningfulness and insights from qualitative enquiry have more to do with the information-rich nature of the cases selected and the observational and analytical capabilities of the researcher than with sample size.

In order to ensure adequacy of data, I used purposive sampling in order to ensure that information-rich cases were included. In general, more than 20 cases are considered an adequate number (271). It is often recommended that data is gathered to the point of ‘redundancy’ or ‘saturation’ (275, 276) – indeed, during the inductive coding process – no new themes arose in the last six transcripts, indicating that thematic saturation was achieved. No new issues arose when re-coding transcripts deductively using the selected frameworks described in chapter 4.

The use of multiple data sources, in the form of field notes, interviews, focus groups and site documents ensured adequate variety – some authors term this use of different sources of data ‘triangulation’ – and equate this with dependability and

consistency (and internal reliability) (269, 270). The more variety in the data sources that one is able to obtain, the greater will be the richness, breadth and depth of the data gathered.

In order to ensure a range of opinions were sought, interviews where outlier data was found were also looked at in detail (220) – this disconfirming evidence, and in particular, transcripts obtained from interviews with two individuals (Chief Investigator E2 and Member of Sponsor University H2) with an interest in sustaining alternative narratives to those sustained by the rest of the sample were carefully examined, and are discussed in the Findings Chapter in section 7.4.2 and 7.3.3 respectively.

6.8.2 Adequacy of Interpretation

Immersion in the data involved transcribing, review of the interviews and source documents in order to get an appreciation as to how the individual parts interrelate. Repeated forays into the body of data in order to develop timelines and map out relationships was an essential component of describing the story. Clarification of the sequence of steps involved in making any kind of decision, or that involved in the propagation of an error leads to a deep understanding of all that comprises the data corpus.

The use of an analytical framework grounded in social science theory – developed and tested for use in other organizational contexts, such as aviation and healthcare – ensured coherence of interpretation (271). The presentation of findings contains a balance of my interpretations and quotations from the participants. It is my hope that

the results are presented in such a way that the reader's understanding of the phenomenon being discussed is clarified and expanded.

6.9 Ethics

As part of this research project, in February 2014 ethics approval was sought under the guidance of my supervisory team at the time. At the time of thesis examination and viva in February 2018 one of the examiners raised concerns about whether proper procedures were followed for ethics approval.

The Dean of HYMS instructed an investigating officer to undertake an assessment of the circumstances surrounding the ethical permissions in place for the research. A formal and thorough investigation took place with consideration given to the training in research methods, written correspondence, supervisory support, organizational circumstances and accounts from all senior members of university staff with an advisory or supervisory role.

The conclusions of this investigation included the finding that the research was conducted following appropriate ethical practices. The key ethics considerations and how each were managed are described below.

6.9.1 Ethics permissions sought

Ethics advice and support was sought from supervisor, Research and Development department, and NHS Health Research Authority (NRES committee for Yorkshire and Humber). A formal letter of enquiry was sent to NRES, and their response

forwarded to supervisors and the Research and Development department of the Trust. The proposed project was classified as audit/service evaluation. No further action was deemed necessary at this point in respect of ethics approval.

6.9.2 Participant support

Each participant was emailed a letter of introduction (attached as an appendix), a statement which described the purpose of the study, and question schedule was included. Supervisor was copied into all emails to all participants, and named as a contact for all participant queries.

6.9.3 Consent process

Informed consent was obtained from all participants. This was recorded digitally and stored responsibly in line with regulations for storage of data (as described in section 6.6.5)

The conclusion of the internal investigation confirmed that this research was conducted following appropriate ethical practices. Following the review of the investigator's report, a panel review concluded that based on the evidence made available, that corrections of the thesis could now take place, and the thesis submitted for re-examination and the examination process for this medical doctorate to continue as normal.

6.10 Ensuring Quality

6.10.1 Critical appraisal

In order to ensure that this research is of acceptable quality, I have utilised the adapted version of the Critical Appraisal Skills Programme (CASP) checklist for qualitative studies (2) (used in Chapter 2, Literature review) in order to appraise this case study in the same way that the qualitative studies used in the literature review were assessed for rigor, credibility and relevance (263).

Using the CASP assessment scoring system, this thesis so far has demonstrated the following:

- There has been clear statement of the aims of the research
- Qualitative methodology has been discussed and justified as part of the methods
- Research design has been described, and justified on the basis of the methods used in previous research in the field, and through consideration and appraisal of alternative methodological approaches
- Recruitment strategy has been described and justified
- Methods of data collection have been outlined, and data sources described.
- The relationship between researcher and participant has been made explicit.
- Ethical issues have been taken into consideration, and methods of approval described.

This describes the clarity of methods so far to be of high quality. The critical appraisal tool will be revisited in the discussion section to ensure that the final parts

of the quality assessment score – Sufficiently rigorous data analysis, Clear statement of findings and Value of the research (transferability) – are also fulfilled

7. Findings

7.1 Introduction

Organisational accidents occur in a system – they have multiple causes involving many people working at different levels within their respective companies and departments. Though these occurrences are extremely rare, these organizational accidents (such as the failure of this trial) can have devastating consequences to populations and individuals that are not directly involved in any way (such as the local economy, and the needs of the potential users of research) (185), and involve considerable financial and ethical waste – particularly where research does not lead to worthwhile achievements (45).

One of the main areas of importance, and one that I felt was essential to explore through this research was that of the ‘whole situation relevant to this event’, or the ‘culture’ of the organization – an issue that is described at length in the literature surrounding error in the aviation industry (43) and in business (277). Culture binds a group together, and has the potential for multiple consequences – it can influence how juniors relate to their seniors, and influences how information is shared, it can influence adherence to rules, and attitudes towards stress and personal capability to produce behavioural norms (“the way we do things around here”). This contributes to the conditions in which an error can propagate, and where accidents can occur.

One of the key attributes of the Model of Organisational Accidents is that it can help to understand how an accident occurred, the errors that were involved, and the culture that allowed these things to happen – assessing whether there were deficiencies and a failure to understand the threats to the trial and the danger that it

was in, whether individuals within the organization felt that communication was adequate, and whether there was a willingness to address deficiencies (185).

Whether, if there was concern or a threat to the trial, whether there was sufficient concern to do anything about it. These ‘Source Types’ – that describe the attitude of an organization to safety information, and the level of response, are described in the second part of this chapter, and help to develop a greater understanding of the challenges this trial faced.

7.1.1 Chapter Overview

Through this chapter I will describe the results obtained through analysis of data – primarily that of interview transcripts, but also through analysis of certain key documents. In Chapter 4 I have described the theoretical approach adopted, and how I have attempted to couch this analysis in social science theory. The first part of this chapter describes the outcome following the application of themes that were derived from the project management literature, namely Robinson’s Clinical Trials Risk Management (11), and the associated ICH-GCP considerations for each phase of the trial.

In the second part, a description of the results relating to Reason’s Model of Organisational Accidents is recounted (38), along with the categorization of the types of error, and how these then feed into Sasou and Reason’s taxonomy of team error in complex systems (39) – it is hoped that this helps to reveal how deficiencies in communication, resource/task management, the presence of an excessive authority gradient and excessive professional courtesy can contribute to an environment where there is a greater likelihood that team error will occur.

As described above, I show the results obtained from applying the themes from Robinson (derived from the project management literature) and ICH GCP to form a descriptive framework to help to

The high level themes for this would be:

- Definition threats
- Planning threats
- Implementation threats

All of which refer to the various phases of the trial, and the associated risks that are inherent with each one. Chapter 4, section 4.3 describes these trial phases in greater detail, and the theory that surrounds them.

In the next part of the chapter, the findings from the application of the data to the explanatory framework – Reason’s Model of Organisational Accidents, are then described.

The high level themes for this would be:

- Types
- Tokens

These would then be further divided into Source Types/Function Types and Condition Tokens/Unsafe Act Tokens. Figures 17 and 18 in Chapter 4 describe these themes and the theory around them.

Appendix 4 demonstrates part of the coding tree, and illustrates how the findings were derived.

7.2 Definition Threats

The definition phase of a trial is described in greater detail, along with a description of all the different phases of a trial, in Chapter 4, which describes the theoretical

approach to this analysis. The Definition Phase covers the events from the conception of the idea of the clinical trial, through grant application and trial design, through to the point at which the grant is awarded.

7.2.1 Trial Design

The dangers associated with an ambitious participant recruitment schedule were compounded by overly restrictive eligibility criteria, a well-known, modifiable risk factor (87, 278, 279)

“look at your exclusions... it’s a page of exclusions and, you know, if you want to run a pragmatic trial with loads of patients, I honestly think... that’s pretty much going to take you out of the loop... I’m sure there’s some long winded justification to each one of them but... every exclusion will take people out of the study” Trial Steering Committee Member D3

Restrictive eligibility criteria made large-scale participant recruitment impractical (design) – The trial was designed in a way to make it ‘simple’ – in that once a patient had been recruited at a centre, the majority of the follow up and monitoring for outcomes would be done by a central office. Unfortunately, the complicated eligibility criteria made the ‘simplicity of trial design’ irrelevant, as there were very few included.

“This is supposedly one of the easier multicentre trials that they would ever be able to do if it was successful. This was not onerous, in any sense of the word.. whether they got that. Understood that. The idea was high throughput.. and high recruitment.. limited amount of work for the actual investigator on the

ground.. because the rest of the bulk of it would be done by the monitoring office.” University Management Team C1

This was a trial that was designed to be solely based in the UK. There was a poor appreciation of the availability of eligible patients within the UK (90, 280, 281). There had been no examples of similar trials having been done in the same disease population that had managed to recruit the numbers that this trial was hoping to achieve. Descriptions of similar trials, with examples of trial inclusion and exclusion criteria and their actual levels of recruitment, are given in the redacted portion of Chapter 3.

“(The Study) was the value of [a treatment] strategy in [disease population] and the total awarded £[Number]million? ... I’m just reminding myself about the sample size ... 3000 patients? So it was pretty ambitious. This is a single country study... There are no precedents of that - I mean I don’t believe there’s a [disease population] study that’s involved 3000 patients, we have enrolled in the UK” Trial Steering Committee Member D3

Unrealistic recruitment projections increased the likelihood that the trial would fail to deliver as expected (internal processes)

“The initial recruitment projections were wildly optimistic and should never have been agreed.” Trial Steering Committee Member D5

Optimism when putting together recruitment projections in clinical trials is not unusual (18, 90, 278) – and predicting recruitment rates is complex, early planning with pilot studies and feasibility work is an important measure that can greatly assist

with trial management (90). There had not been a period of time to pilot this study within the host institution in order to gauge feasibility. The protocol document did discuss previous trials where the Chief Investigator had been involved in the design and conduct of the trial, in the same disease population, looking at similar treatments

“(Trial 1) was a pilot, (publicly)-funded study specifically designed to find out whether a trial comparing (treatments) in (disease population) was feasible. In (Trial 1), recruitment was slow and it became clear that investigators, although intellectually persuaded, were still unable to randomise patients in large numbers, either because they felt emotionally that it was not in the patients’ best interests or because the patients refused. The (Trial 2) trial may also be considered a pilot for this study. Use of (an additional treatment arm) and an administratively complex trial design hampered enrolment. Thus, lessons learnt from previous trials have been used to develop a much more robust and greatly simplified protocol.” Study Protocol Document

Piloting and feasibility work is important to answer questions regarding participant recruitment and retention (282-284), plan for administrative variables such as the willingness of physicians and patients to participate in the trial (285) and is now a recommendation by funders of publically funded trials (such as the NIHR) that feasibility assessments are used to set targets for recruitment, and are recommended to aid the grant review process (286). Therefore, basing trial design on his previous work, the Chief Investigator was demonstrating issues encountered with recruitment in both previous trials that had been used as examples of ‘pilot’ work. As neither of these examples had successfully recruited, this increased the risk of inadequate

recruitment in this trial. Therefore, the logic that an internal pilot trial was not needed was flawed.

7.2.2 Standard Operating procedures

The over-riding definitional problem was that the study had been designed to minimize costs rather than meet objectives. For instance, the monitoring resources which ensure recruitment to industry studies (through provision of site based study personnel (77) for example, to drive local trial activity) were absent, meaning enrolment was reliant on goodwill. Procedures were designed to minimize cost – potentially increasing the risk of a failure of return.

“(The Study) had a number of unique things which allowed a multi-centre study to be done with limited resources ... there were barriers to doing that because of the relationship you had to have with the individual centres; so unlike the conventional drug multi-centre study where you have someone visiting every week as a monitor, you relied on the motivation of someone...”

University Management Team C2

7.2.3 Market Potential

Market authorisation of new generation technologies for the same indication ensured that the trial interventions had no safety or efficacy advantages over competitors. It is, unfortunately, not uncommon for the success potential of trials to change as competing therapies come on to the market as occurred in this case. What would have been considered a worthwhile question by clinicians at participating centres becomes less so as formulary changes.

“From a medical point of view.. maybe there were other factors involved... maybe they were thinking – hang on, maybe there are other things that are superceding (Investigational Products) maybe we don’t need the answer to this question now maybe there were other things going on there” Trust Employee B1

However, the key interventions that were being examined as part of this trial involved the use of simple, cheap medications – testing of new generation technologies for the disease population would depend on drug industry investment, which may mean more expensive treatment options being tested

“It’s a shame because it might actually put off funders putting money into this type of a study which, you know, because they were trying to look at both things weren’t they, the study and how you do it without having to bring big drug companies in as well” External Site Focus Group 11/12

Clinicians felt that the clinical question that was being addressed in the trial was necessary and important

“It’s an absolute shame because I think it’s an important question that (Chief Investigator) was trying to address” Trial Steering Committee Member D4

“I think that the scientific question was really important and it could have made a big big difference to the management of patients with (disease condition) and now we’ll all be staying on (current standard treatment), right?” External Site Focus Group 11/12

7.2.4 ICH-GCP Violations and Shortcomings

Value for money for research

The main research funder plays a critical role in assuring the quality of a study. It will normally take the lead in establishing that the research proposal is worthwhile, of high scientific quality, and represents good value for money (176). This assessment compares the potential benefits with the resources that the study requires, and funding decisions often depend on priorities, often dictated by the burden of a disease, and acceptability of intervention (45).

“There are a number of factors that have to be considered when deciding whether a research study is to be funded, the costs of the intervention, how important the question is, how many people are affected by a disease. It is more difficult to justify funding an expensive treatment in a rare disease that doesn’t really affect anyone’s quality of life. And when dealing with public money. It’s got to be a careful considered decision” Funding Body

Representative A1

“and I think the (funding body) really did miss out on this trial. Any outcome.. pro (treatment).. against (treatment).. the same... would inform clinical practice... it was a really pragmatic, well designed study in that respect.. it’s a shame to have missed out” Trial Co-Applicant G1

7.2.5 Definition threats summary

- Restrictive eligibility criteria made large-scale participant recruitment impractical (design).
 - Unrealistic recruitment targets increased the likelihood that the trial would fail to deliver as expected (internal processes)
 - Market authorisation of new generation technologies that had the potential to be used for the same indication ensured that there was a chance that trial interventions had no safety or efficacy advantages over competitors (market potential)
- ICH-GCP (definition)
- Value for money for research – no concerns raised

7.3 Planning Threats

The planning phase of a trial covers the event from the grant award, through the trial set-up stage and the establishment of ethics permissions, to point at which the first patient is recruited and included in the study.

7.3.1 Site Selection

The determination to run the study in the UK alone, meant the CI did not have flexibility over site selection, something generally associated with positive outcomes in clinical trials (110). This meant that the team was obliged to persist with centres that found difficulty meeting service support and treatment costs.

Working with sites that had no previous experience of working as part of research trial did prove challenging. Engaging with primary care in particular is something that has been explored at length in the literature (287) – of course there are many primary care centres that are readily able to be involved in research, and are able to recruit participants – and the main characteristic that matters in terms of engagement with a GP practice, is previous research exposure. Unfortunately, in this case, with

high targets of multi-centre recruitment, the Chief Investigator did not have the luxury of choice.

“Well I think that as all of these patients were in primary care, it’s entirely reasonable to do that but just while we’re talking about that, what was the kind of success rate in those primary care centres? They were very keen to get involved and attended the investigators’ meeting and that sort of thing. However, in practice there was only one GP surgery out of the twenty or so centres that were ready to go by 1st January. Well, you know, I think that that’s probably what we would have expected a lot of, enthusiasm, but not really delivering.” Trial Steering Committee Member D4

7.3.2 Availability of services

The true deliverable of a clinical trial is information, and that it is accurate, reliable and secure. It is essential that IT planning is involved in the earliest stages of trial planning in order to avoid undue delays and increased costs (288). Extraneous or ‘non core’ data (data that are not associated with either the primary or secondary endpoints) inclusion in a trial database generally results from a loss of focus, and can cause increased cost and time delays (289).

“(The Sponsor) kept stepping in and asking for all sorts of extras for the system-the automated adverse event reporting, the automated deviation reporting, late returns of questionnaires etc.. so we added all of that into the system...which bumped the cost up of the system... we still ended up with a brilliant system ... about 6 months late...” University Employee H2

“We did plan for having a database – from our point of view and that of myself and (Chief Investigator) at the time.. we were kind of new to this.. and kind of oblivious to a degree of what the real costs were and I think we built in.. 20.. 30 thousand pounds worth of costs for the database development.. and when it actually came to fruition we were actually looking at a bill of about 68 thousand..” University Management Team C1

7.3.3 Staffing

The trial struggled to appoint a project manager – a timeline of 6 months was built into the budget and timeline projections in the application and contractual agreement, however, there were considerable delays in finalizing job descriptions, advertising, and finding a suitable candidate.

“I’m not sure what you could have done about appointing the project managers. The 6 months that had been built into the plan in the project... was... I think... reasonable. I don’t think you could justify anything longer.”
University Management Team C1

In this report based on the Prehospital Use of Plasma in Traumatic Haemorrhage (PUPTH) trial, it was found that without a trial management structure, the early stages of the trial were characterized by inertia and organizational confusion, until a management system was introduced (288).

“About 15 months after the grant was awarded.. University HR finally got around to advertising the job of the project manager. Initially... the awarded

*the job to a guy called ***(PM 1). He withdrew as soon as he started.”*

University Employee H2

“The post was re-advertised 4 weeks after the candidate’s withdrawal. There were 3 applicants, but all withdrew prior to the interview date

A project manager was then appointed from a recruitment agency, 18 months after the grant award.” University Management Team C3

“The chap that was in first (PM 2). And he went off with the Trial Master File – and was in post for less than six months, before leaving. And then, (PM 3) was brought in, to help, as sort of assistant project manager - she had never managed a project that size before” University Employee H2

Additional information was obtained from the University HR department, and a separate interview took place. Additional documentary evidence was offered – in the form of emails and correspondence around the appointment of the project manager – and more details are given in the quotes in section 6.3.6 Adequate resources > ‘Staffing’ – which confirm the sequence of events around the appointment of the PM, and shows that there were no undue delays in process, but that there was difficulty in having the right candidate apply. H2 held a dissonant voice around the subject of PM recruitment:

“The problem...the root cause is that the university will not pay trial project managers what they’re worth, and think that its only a band 7 job for something, where it should easily be a band 8. You’re trying to control a 3 and a half million budget...” University Employee H2

7.3.4 Clinical Trials Unit

The obligation to work with a trials unit, placed on the chief investigator by the funder with the intention of mitigating risk, was expressed by him as a liability in terms reminiscent of classic critiques of bureaucratic intermediaries (290) and revisited in a recent BMJ debate on the utility of CTUs (101).

“All of that professionalization of bureaucracy increases the expense of running clinical trials and clinical trials now need their own bureaucracy in order to fight the regulatory bureaucracy whether it be ethics, R&D or indeed from the regulators themselves” Chief Investigator E2

“But you are astonished by the degree of inertia and bureaucracy that people show. Its not the investigator of the individual site - it's the people who pass the paper around - and they would come up with all kinds of barriers; so what one needs to do is to have a clear, SOP or whatever to deal with that. The trouble is that the NHS is a communion which changes all the time so you may come up with a trial and say - we'll do it this way - but by the time it's actually there that system no longer exists. Then you've got to deal with some other bureaucratic nightmare” University Management Team C2

In a survey of factors influencing site selection in Europe, Gehring et al found that the reason why a lot of potential sites may be excluded from a trial, may in part be due to the hidden costs associated with excessive administration time needed to get individual sites up and running – these are those characterised by time lost through layers of bureaucracy, slow recruitment by sites or poor overall site performance. Hence, the importance of not only bureaucracy, but also of the level of training and trial expertise at sites (291).

CTUs provide an infrastructure and experience(101). Accumulating such experience is costly and time-intensive (102). And establishing a new CTU, or fulfilling all the functions of a CTU in an academic research department requires a considerable amount of pooled experience, and staff resources, such that a trial does not slow, or stop due to staff sickness, leave or similar (100).

“So you didn’t have an infrastructure? Trying to set up an infrastructure, you know, for a very massive trial, it’s really tough. Oxford also run a [disease population] study, but you know, Oxford has an infrastructure of 200 staff and obviously not all of them are working on one trial but .. They always had to battle against exactly the same things in terms of, you know, any ethics approvals, getting R&D sign offs and all of that sort of stuff” Trial Steering Committee Member D3

Had the Chief Investigator of the trial engaged with a CTU - to be fully involved in the trial, they would have been obliged to re-staff with an experienced study manager. As Merkus mentions in a recent letter to the BMJ, “Academic CTU support has the advantage that long-term continuity of staff is ensured and multidisciplinary knowledge and expertise are maintained and continuously improved, in contrast to a single project manager working under standalone conditions” (292)

*“It massively suffered from this decline of CTU involvement. One project manager – from Pfizer - I think he lasted a week, then it was another project manager from another agency, and he lasted, that was *** (second project manager) and he lasted about 6 months - and at least he could train up *** (third project manager)... a little bit.. But it was just too slow... before the study started” Trust Employee B2*

The sponsor (host) organization were not able to accommodate a project manager – or have any one that could take on the role once a new project or study had commenced in the department.

“An issue was with the management structure – in the days when (The Study) was being set up the organisation was not that of (Medical Research Dept Of University) – which was organizationally quite different from (Medical School). There wasn’t in existence at that time, a core staffing for project managers for new projects in the department.” University Management Team C3

7.3.5 Regulatory Bodies

“The way these grants are actually structured, there are those two big funding gaps, service support and excess treatment, and both of those can, you, know, basically cripple a trial and then, I think, the contracting process with NHS trusts still pretty complicated and the approvals process, you know, it’s got pretty complicated, so that can take quite some time.” Trial Steering Committee Member D3

Research priorities and identifying organizational motivations to see a project through to completion is an issue, especially when attempting to conduct a multicenter clinical trial. Although the interests of the central trials team, and those of the local satellite centres do intersect, they do not completely overlap – so the help and assistance required from the local team in order to conduct a study is sometimes less than anticipated.

“One of the issues is that clinical research is not a priority for the NHS organisations that actually pay for it, not with service but there is prioritisation given to research at an NIHR level which drives important work but then actually implementing that becomes difficult because the people further down are not interested in research. More further down and people at a different level, CCGs as was, are not interested in seeing the research through to completion.” Trial Steering Committee Member D4

Many projects do experience delays – in particular when trying to open up several sites as part of a multicenter trial. Delays can be numerous and frustrating (98), and can cause a considerable impact to the cost of a trial, (111), and have often been cited as a reason for trial failure (97, 293)

“It did seem that everything that could possible go wrong did go wrong in terms of the administration bureaucratic side of things, the classic example would be the ethics committee having already twice approved something in the protocol and decided not to approve something and that led to another 60 days delay and again was something that was probably the final straw that broke the camels back.” Chief Investigator E2

External site set-up and initiation was time consuming and had a number of stages that were associated with delays – particularly those where the site was less familiar with the permissions and set-up process involved. Levett et al examined the recruitment rate in a randomized controlled trial, preterm prelabour rupture of membranes close to term (PPROMT). Their findings suggested that for trials to recruit effectively, participating centres need to have a defined research trial structure which supports the site investigator. In the case of investigator-led, non-

commercially sponsored trials, if the investigator is engaged with the research question and has engaged other staff to fulfil their commitment to recruiting to the trial, the site will recruit well and consistently (294).

“I think the sites, there are so many of them and the SSI forms were nowhere near being complete, I think that probably could have been handled better. I mean there were so many. I think that was the problem. We just needed to set up sites as quickly as possible and it was a bit chaotic. It could have been controlled a little bit better doing so many at a time, because really to get the sites we needed, we needed every single SSI form ready by 1st August and everything needed to be ready to go and be sent out” Core Trials Team Member E3

There are a number of factors to be taken into consideration when choosing sites that make up a multicentre trial. Centre characteristics that are associated with better recruitment include those with academic and research connections, and are ‘Research Ready’ by way of structure (109)

“From a broader perspective (it was) ambitious in terms of the number of centres, a smaller number of centres and more patients, that would be the better thing to do. So get involved your proper bona fide researchers to start rather than trying to do maybe forty practices. And if there’s no pedigree in research, these people aren’t going to do it so I think the question was important.” External Site Focus Group II/I2

7.3.6 ICH-GCP Violations and Shortcomings

Experience of the Chief Investigator

The Chief Investigator was an expert in his field. He had applied for grants in the past, and had a good record of securing substantial grant awards from charitable trusts, as well as having involvement in the design and implementation of multicenter trials. This, however, had been the largest single grant, from a publically funded grant-giving organization that the Chief Investigator, and the Sponsor organisations had ever been awarded.

“Then I’m not sure about the experience of the group that were running this trial, obviously (Chief Investigator) is a very experienced investigator and trialist and he has run several trials, independent of a commercial sponsor”

Trial Steering Committee Member D3

“My personal take on this is that I’ve known (Chief Investigator) vaguely for many years...we don’t work in the same area but I’ve seen him talk, and I know he’s been involved with some very important (disease area) studies but I think he was just very used to doing things in the way that trials used to be done before the (funding body) started funding its own trials. And he didn’t understand, that... the (funding body) doesn’t work like that, it works in a very specific way and if they want to close a trial down then they’ll close the trial down.” Trial Steering Committee Member D1

Being a successful, busy, academic individual, managing to win grants successfully and innovate with ideas for new treatments for certain conditions meant that the Chief Investigator was involved in multiple projects at any one time – and had little time, or experience in post-grant-award management or administration

“I recall speaking to the previous dean, suggesting that although (Chief Investigator) was a gifted clinical researcher, that appointing a manager to help with his affairs would be good. I am very fond of the man, and he works very hard, but thinks that once a grant is awarded, that everything else will just fall into place and the study will just happen. And things don’t work like that.”

University Management Staff H1

Attempting to manage a clinical trial without strong project management expertise or research infrastructure in place, meant that there was no-one that was able to take on management responsibilities –

“What a lot of investigators would do is to appoint a senior trial co-ordinator, or manager or whatever you want to call it, in the trials unit, who runs the trial and then they would appoint a separate person, often a person with a PhD, who would work with the chief investigator and provide more academic support. And it’s quite nice, as a chief investigator, it means you can step back... And you’ve got a team and you don’t have to worry about doing anything. You can focus much more on the trial itself, and the clinical aspects of it rather than worrying about, you know, is there enough drug in pharmacy this week.” Trial Steering Committee Member D1

And difficulties were encountered when the Chief Investigator attempted to manage aspects of the trial

“The Trial suffered from not having the right expertise, possibly also, the personalities of the people involved... the CI was very hands on. More than any other of the CIs and PIs that we’ve got in the organisation - in the sense that we expect CIs to make the decisions, but not to manage and micromanage

*to the level that was happening. It does hinder the decision making.” Trust
Staff Member B1*

*“(The Chief Investigator) thought they could control the whole process and
they will get what they want, well, that’s a little bit of the wrong attitude,
because what you need to do is to put your faith in the people who are helping
you - leave them to get on with their job and only shout at them if they’re not
doing what they say they are going to do.” Trial Steering Committee Member
D1*

Suitability of research environment

The research environment – the sponsor organisations as a whole were new to the process, and did not have the experience of running a trial of this size and complexity

*“I think the department as a whole was probably a bit ill equipped to handle
some things so big and I think the Trust were ...I think (Head of R&D) sort of
said it was a big learning curve for them and you know, if the study had been
in Leeds or another big hospital, there would have been a lot more expertise
there to call from so I think everything was started from scratch pretty much.”*

Core Trials Team E3

There was Clinical Trials Unit involvement at the beginning of the trial, following grant award, on an advisory basis. Their support was withdrawn prior to randomization of the first patient, which was likely to have changed the expertise and experience available to the trials team to a considerable extent.

“When I was asked to work on it I was told that the funding was half a day a week to give advice when required... I was spending a lot more than half a day a week, sort of just even reviewing the protocol. I gave input into that, into the CRFs, so I think I met with (Project Manager), and they sent me stuff and I sent them examples of what we had done, and then sort of reviewed stuff again” CTU staff member F2

“So (the) CTU’s involvement, well, they withdrew. And I think that was when the (funding body), well one of the main factors the (funding body) didn’t like.

I think as well that the (funding body) probably didn’t have the confidence that we as the central monitoring office, had the experience to deal with the trial, cos really we were acting as a CTU. Everything was on the right lines, although ten times slower than it should be because I was spreading myself thinly” Trust Staff Member B2

The likelihood of delivering a trial improves with the involvement of a CTU, in particular, as in this case, that there was not a history of running large scale clinical trials from the sponsor organisation, and there was not a pre-existing infrastructure of expertise and staff resources such that planning and implementation of the trial could commence (101)

“Well, I can tell you, without a trials unit it won’t work. With a trials unit it could work but I think with a good trials unit, the probability, assuming the study design is appropriate, you know that you’ve got a reasonably high probability of delivering the trial, now whether you were to deliver on time or

not is very difficult because the research environment in the UK is not conducive to academic studies delivering on time” Trial Steering Committee Member D3

Although a named CTU was involved, and available to give advice as needed, based on a report that was commissioned by the Sponsor University, 2 years after grant award, as part of an assessment of trial progress - the following comment was made.

“The reviewer is not convinced that the current staff, who are inexperienced in setting up and running CTIMPs, fully understand the volume of work which still has to be done, or how to do it in a timely, efficient manner, the reviewer has concerns over the willingness of the trial team to accept the intervention and advice from an external CTU” Comments from external review report commissioned by Sponsor University

The Chief Investigator reflected on learning points following the closure of the clinical trial, and the role that CTUs can play in clinical trials

“To realise you should work with a CTU. I would never in the UK take on a similar study without CTU or more formal support. They have the SOPs. They know the bureaucratic barriers that are not obvious to even a clinical trialist who’s working in the area that there are lots of obstacles to success and they know them. They’ve come up against them before. They know how to solve them, especially when they are top notch, and there are not many top notch CTUs in the UK. I’ve done a lot of soul-searching and exploration and indeed initiating new clinical trials, having learnt a lot of the mistakes from (This Trial)” Chief Investigator E2

Adequate Resources: Arrangements to initiate and manage the study

The main issues here were that the sponsor organisation was initially supported by the involvement of a CTU, on an advisory basis, whilst infrastructure, accommodation (offices) and staff were appointed.

Staffing :

Appointment of a project manager took over 15 months. A 6 month time period was written into the grant application. The grant was awarded in September (year 0)

*“A job description was outlined by March (year one). It went to the TSC and CTU and there was a delay of 4 months whilst this was finalized. There was difficulty in coordinating different opinions and stakeholders requirements in July (year one), there was a draft job description obtained from the (funding body). This was then sent to the University Department, and it was approved. A candidate, ** was interviewed and identified as being an ideal candidate for (this trial) Contract was then offered, on the August (year one). Planned start date was October (year one). Candidate withdrew day before start date. PM job was re-advertised November (year one) and there were no applicants. Candidate found via recruitment agency February (year two). This candidate left position after 3 months, in May (year two)” University Management Team*

C3

Attracting experienced project management staff was something that the Sponsor University was responsible for – and getting project managers that were adequately experienced was also an issue. The following quote is from one of the Project Managers that had been appointed to run the study

“I’ll be quite blunt - a lot of the time I was making things up as I went along. I think that if this study was run somewhere else, (had I applied for this job) I don’t think I would have even got a sniff, I don’t think I’d have even got an interview, and I don’t think (Other PM) would have either and I think that experience was an issue – neither of us had ever done anything like this before” Core Trials Team E3

Provision and appointment of enough staff, that are adequately qualified to perform the tasks required for a clinical trial is a core consideration of the ICH-GCP guidelines (37). The principles and conditions of Good Clinical Practice must be adhered to according to law – and ensuring that all staff on the delegation log are trained in GCP is a legal requirement (295). Following the commencement of the trial – progression was slow, the sponsor organisation (university) commissioned a review of the trial, undertaken by a representative from another clinical trials unit – some sections of the report are shown below

“Of the CVs reviewed, only the Chief Investigator has GCP training listed”

“Reliance on a single member of staff – The current project manager is in an isolated position with no other senior member of staff available for cover or support, apart from the CI, who sees his role as science rather than the day-to-day running of the trial set up” (External review of trial progress commissioned by Sponsor University)

Accommodation:

Finding adequate accommodation for trials staff took the sponsor organisation a considerable amount of time – following the appointment of a project manager,

office and desk space still had not been identified from which to run the clinical trial. Offices in which to house the study were identified over two years following the grant award.

*“So in the grant application we built in costs for using the ** offices - which at the time we were told was an option - we built our costs around that. When the grant was awarded, and we went to firm that up, we was told that because the way that that particular building was funded that we couldn’t actually use it. So, we had to go out and try and find other accommodation and of course other accommodation was grossly higher in cost. So we went externally we looked internally we contacted university we contacted the trust, we scrambled around for any kind of accommodation. No one was that supportive. We got to the point where that the then project manager was then looking at rooms above a pub. Which I kind of said no to, but it was kind of what was available and what was on offer that we could afford. So I think that there was a lot of frustration at the time. And we had the project managers basically working out of a hotel room. Which says it all really.” University Management C1*

Later on there were concerns that the accommodation and staffing levels were not adequate for the potential volumes of work that would have come through the central monitoring office.

“I think the sites that we got up and running did reasonably well. I think a lot of them did better than I was expecting and I think given that if we were allowed to keep going we could have kept recruiting patients but I don’t think we probably could have coped with the volume, not in that environment

anyway, we needed a bigger office and more people than the grant would allow for I think.” Core Trials Team Member E3

Time planning

According to ICH-GCP, the Chief Investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period (37). Targets for recruitment were set and revised during regular meetings with the funding body – and were agreed to by the Chief Investigator. They were thought to be ambitious, and indeed were not achieved by the trials team during the course of the trial.

“Given the personalities involved, I think it would have been difficult to intervene. But the key failure was to agree to targets which were impossible, If that had been addressed, and it was only an exchange of emails. I know I didn’t look to see what the target was, because I assumed that sensible targets had been set.” University Staff C2

*“Yes, I think the core team I think didn’t believe that actually the ** (funder) targets were immutable targets and I think that that probably contributed to the fact that the targets weren’t met because attendance to trying to meet them was left, I think, too late.” Trial Steering Committee Member D2*

Ethics Approval

The sponsor R&D department spent a considerable amount of time advising on, and approving checklists, consent forms and methods for safely monitoring external sites as part of this study. Their inexperience meant that there were delays, and that, on reflection, they were cautious. They also had little in the way of experience in

running a trial such as this, answering the inevitable queries that arise as part of the approvals process, or giving input into novel database design.

“The lessons to be learnt are -we need to break down the barriers of these institutions. And say, we would like to make this study a success. But there are some unwritten rules, and one of those rules is that the law is the law - if you think that we are being over cautious on particular things then let us know, but offer us a solution. Offer a viable alternative for reassurance of the organisations that we are going to reach the same endpoint, allow us the time to seek advice externally” University Staff Member B1

“The default position was - this is complex, this is new, this is outside of our comfort zone. So the Trust default position was - start with the most cautious route, and work your way up, and even then. We had no baseline to compare against. We hadn’t run another study like this before” University Staff Member B1

7.3.7 Planning threats summary

- With a large sample size, restricting recruitment to the UK meant that unsuitable as well as sites that were research-ready (in terms of infrastructure and treatment costs) sites produced quality threats (investigator suitability).
 - After refusing more than tokenistic involvement of a registered Clinical Trials Unit, setting up alternative trial infrastructure from scratch was impossible within the timescale (staffing).
- ICH-GCP (planning)
- Experience of Chief Investigator
 - Suitability of research environment
 - Adequate resources to initiate and manage the study

7.4 Implementation Threats

The implementation phase of a clinical trial includes the events from the recruitment of the first patient, and ongoing implementation according to the planned protocol. It is this phase where a trial can face a number of risks, some of which can be quite difficult to predict. Issues such as the availability of eligible patients and the safety of the intervention being assessed can be considerable risks to the trial at this stage. Compliance to the trial protocol is recommended to try and mitigate the risk of adverse outcome (11). It was in this phase of the trial that the case study showed evidence of not adhering to the protocol and fell considerably short of its projected recruitment targets. The notice of closure was given, and the study was closed. The implementation phase usually comes to an end with the 'last patient/last visit' point of a trial, following completion of the recruitment and protocol with all participants.

7.4.1 On-Site Monitoring

The sponsor organisation – the hospital trust – did not have any previous experience of running a trial of this size and complexity. Added to this, the chief investigator had attempted to cut costs by introducing a relatively novel system of GCP-monitoring – central monitoring – which was new to the sponsor representatives in the R&D department.

On-site monitoring involves sponsor representatives or delegates visiting research sites to identify data entry errors / missing data, check that study documentation exists (especially consent forms) and assess compliance with the protocol and drug accountability. Central monitoring attempts the same activity remotely (296). Since the case study trial, evidence has suggested that on-site monitoring often adds little in

terms of regulatory compliance or patient safety (25, 297), and regulators have moved towards reduced on-site monitoring for lower-risk trials (298). However, at the time of the case study trial, on-site visits were *de rigueur* for drug trials and developing reporting protocols for trial procedures, such as consent and adverse events, took months.

“One of the things that (The Trial) provided which was also a very time consuming thing was the idea of the central monitoring processes. Which were again, at that time a fairly new concept.. you know traditionally, it was on-site monitoring.” University Staff Member B1

“I think asking centres for the first time in their lives to take on a sponsorship role of multi-centre clinical trials and being very scared of the MHRA and detecting SUSARs and SAEs etc and just being super scared about doing anything wrong, they make the biggest blunder of all and that is killing the study. We had something like a 12 month delay while the R&D office decided what would constitute an appropriate form of adverse event sign off and what indeed would constitute adverse events. So again not something that was facilitating clinical trials but rather obstructing them. All of them surmountable with time or with more resources, but more resources and more time wasn’t made available.” Chief Investigator E2

7.4.2 Investigator motivation

Levett et al suggest that with investigator-led, non-commercially sponsored trials, there is often little consideration paid to the systems requirements for sites to implement the protocols effectively. As a result, the clinicians who are collaborating

in trials are often isolated and have little support or guidance, and trial inertia becomes evident (294). This quote is from a co-applicant, and site-based principal investigator.

“My work, predominantly, is that of a clinician. I am interested in research, and do try to get involved in projects that interest me, or that I feel might help colleagues and answer important questions of patient treatment. What I have found is that research is very expensive, and involves a great deal of investment and commitment, but that the rewards are not always immediately apparent.” Co-Applicant G2

In the case of this trial, it was noted by the Chief Investigator – quoted here, that those sites that had completed site initiation first – without those delays – were those that were recruiting well.

“Those sites that were up and running were recruiting at or above target, it was purely a delay in getting the sites up and running that killed the study and that has got nothing to do with doctors and nurses” Chief Investigator E2

This is in contrast to what was reported in the focus group interview that took place with the recruitment team at another centre that was recruiting to the trial.

“I believe we were one of the highest recruiting centres and we started slowly. Our numbers at that stage were very small, so if we were one of the highest recruiting centres, I can understand why anybody then from the outside might think -well they’re not going to meet - however many, three thousand, in the timescale” External Site Focus Group 11/12

However, when the trial was struggling to recruit, the Sponsor organisations were notified that the funder had given notice to the Chief Investigator regarding the closure of the trial. At this stage, a senior member of University staff was brought in to manage the study in place of the Chief Investigator

“I think the personnel responsible from the top to the bottom were not motivated so there was a lack of effort. Certainly when I took over the weekly meetings there was an attempt at improving motivation, and it did work to a certain extent but I think there were difficulties - with the Chief Investigator and the clinical trials management team getting the required work done”

University Management Team C2

A number of stakeholder groups that were involved in the trial, were not informed that the trial was in difficulty – keeping communication open between clinicians and trial coordinators is seen as an important factor in improving motivation and recruitment, such that they feel ‘Partners in Research’ (25)

“The point I would make is that the communication among, you know, I don’t believe I had a particularly important role in this, but the communication was quite poor I think, to be frank, so I don’t know whether there were regular meetings, was there a steering committee, you know, these sort of things, if there wasn’t a trial steering committee was there a sort of engine of senior academic investigators who were actually pushing this forward, apart from obviously (Chief Investigator).” Trial Steering Committee Member D3

“I had no idea that the study was failing to recruit. And I was a grant co applicant. Had the (funding body), or (Chief Investigator) told the grant

holders of the problems, we could have maybe changed things a little bit. So I wasn't aware that the trial was in difficulty” Co-Applicant G1

As well as a lack of communication between departments and the stakeholder groups within the organization, there was the comment that there could have been the ability for the university sponsor organization to be able to offer practical help. It is difficult to be able to say whether the lack of communication was in part due to lack of cognizance, and appreciation of how the trial was under threat, or whether, despite knowing that the trial was failing to achieve the planned milestones, and was failing to progress as hoped, that there was no coherent response to this important information, and counsel was not sought through communication with the sponsor.

“My understanding was that the project was struggling, but at no point was (University Research Department) approached for advice or help. There is no specific way, but through (University Research Department), there were a number of professors and very experienced researchers that had managed large projects and grants that may have been able to offer advice and support. The project was in trouble, and (Chief Investigator) did not ask for (University Research Department) help after a couple of months of not being able to get anywhere. The first I knew about it was through (Head of Research Professor)’s involvement, and that came about following a letter, which you have probably seen, from the (Funding Body) that alerted all of us that it was in real danger. My understanding was that (Head of Research Professor)’s involvement helped enormously, but not enough” University Management H1

7.4.3 Funding Body

The funding body that supported this trial is a public-sector body– and the level of scrutiny is high. They enter into a contract with the supplier, which is the University in this case, in order to get the Chief Investigator (who in turn enters into a contract with the University) to run the clinical trial.

“The (Funding Body) – [they are very strict once a grant has been awarded] - You submit a protocol and you submit a timeline to recruitment and that is all contractually held to. And they take a very formal view of recruitment targets and they have no hesitation in stopping a trial if it’s not recruiting or they feel it’s never going to reach target” Trial Steering Committee Member D1

The co-sponsorship between University and Hospital Trust is not an unusual one, although some countries, such as Spain, do not allow it (299) in order for only one legal entity to take overall responsibility for a trial. In the case of this trial, the grant was awarded to the University, and the contract for delivering the trial was also signed between the funding organization and the University. The obligation for the Hospital Trust, as care-giving organization, is that of monitoring the safety of the study participants, through ensuring guideline, GCP and protocol adherence.

7.4.4 Patient recruitment

There were issues over protocol compliance and the trial’s compliance with recruitment targets. Recruitment of other sites and trial participants fell short of projections that were put together by the Chief Investigator.

Trial steering committees (TSC) form part of the oversight for an RCT. Although no formal timescale or minimum recommendations for meetings is stipulated, TSCs

typically meet every six months (179, 180). Over the four year period between grant award and trial closure, one would have expected around eight meetings of the committee. TSCs are independent individuals expected to monitor and supervise the progress of the trial, review information from other sources (such as related trials), communicate the progress of the trial to relevant parties (such as sponsors and funders) (177). In addition, they are able to advise the Chief Investigator, and offer support through their collective experience (179, 180).

“How often did the steering committee meet? Twice? The steering committee should have been meeting, in a massive panic, on several occasions to actually to find why it wasn’t working out.” Trial Steering Committee Member D3

7.4.5 Availability of eligible patients

Prior to commencement of recruitment, the trial had been discussed with investigators, one member of the trial steering committee suggested

“Pledges of clinical support was such that the recruitment goal of 3000 patients over just 2 years seemed achievable, particularly given the broad entry criteria and the asserted abundance of suitable patients” Trial Steering Committee Member D5

But in reality, predicting the number of eligible patients for a study is extremely difficult, and it is easy to overestimate (300). As mentioned earlier in this findings section, there had been no feasibility work in order to predict patterns of recruitment and outcome, and a previous multicenter trial that had been headed by the Chief

Investigator in the same patient population, based within one country recruited less than 300 participants in an equivalent timescale.

7.4.6 ICH-GCP Violations and Shortcomings

Arrangements for monitoring

A database was commissioned for the trial – it was expected that the majority of patient data could be stored in the database and information from the central monitoring office and trials team inputs – such as patient interactions and follow-up phone calls - could be entered in directly. The trials team did not have experience in commissioning such products, and a lengthy tendering process, and requirements changing after the software had started to be written led to delays, and a database that was considerably higher in cost than anticipated.

“The cost at the start of the project was for a simple database, and that would have covered it the cost for the system to manage the study - which is what you ended up with. Okay, so that was three times, four times the cost of the basic database. And of an order of - maybe a quarter - Of maybe what it would have cost, should we have gone for a commercial package – example... I mean... I actually asked a couple of the main clinical trial database providers... like macro... and a couple of others I think, what they would charge in terms of licence fees. They were talking 300 thousand.” University Employee H2

Part of the GCP considerations when involving an external organization, such as a company that will write and provide a database for a trial, is to ensure that provision is made for a formal agreement as to the terms and conditions (37), as well as the

specific requirements for a database. Part of the external review that was commissioned noted that there was no evidence that this had taken place in this case.

“Key pieces of work, such as the development of the database are not covered by an official contract, and terms and conditions had not been defined.”

(External review of trial progress commissioned by Sponsor University)

Essential documents

A responsibility of the Investigator includes the maintenance and retention of core trial documents, including the ‘Trial Master File’ (TMF) such that they are available for inspection by the regulatory authorities (37)

“But I think there were difficulties with the clinical trials management team getting the required work. Well, there was a chap in first, wasn’t there (Project manager) and he disappeared off with the trial management file. He had a breakdown so that didn’t help.” University Staff Member C2

“... (Project Manager) - he took the trial master file home with him.. and lost it, he also lost a university laptop... with... with all the study information on.”

University Management Team H2

“Other serious problems which were noted by the reviewer included poor adherence to the principles of GCP, the most serious example of this is the disappearance of the trial master file (TMF) which seems to have been taken home by the previous project manager and has not been seen since. The reviewer was shocked to see the casual acceptance of this extremely serious situation and feels it indicates a lack of understanding of the principles of GCP

and the purpose behind them” (External review of trial progress commissioned by Sponsor University)

The Medicine and Healthcare Products Regulatory Agency (MHRA) regularly inspect clinical trials with investigative medical products (CTIMPs) every two years. There was no MHRA inspection whilst the trial was active, but had the trial been inspected, the absence of a complete TMF would constitute a ‘Critical Finding’ – considered ‘Totally Unacceptable’ by MHRA standards, the trial would have been closed immediately (301).

7.4.7 Implementation threats summary

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| <ul style="list-style-type: none">- Poor consideration of ICH GCP, meant study was less likely to be conducted in an ethical and legally acceptable manner (GCP compliance).- Trial documentation went missing (investigator responsibility)- Staffing, accommodation (sponsor responsibility: reasonable environment)- Database provision (sponsor responsibility: monitoring)- Despite the efforts of site teams, inadequate numbers of eligible patients were recruited – compromising the scientific validity of the study (Eligible patient availability) |
|--|

7.5 Mapping of results using the ‘Model of Organisational Accidents’

7.5.1 Types and tokens of failure

In the following tables, the interpretation and mapping of interview and document data into the ‘Types and Tokens’ framework is illustrated, with results separated into the subheadings as in Figure 19.

The host organisation appeared to be motivated to observe regulations but had not ensured that adequate resources were allocated to do so (Table 17: ‘commitment’). Its information system was inadequate and there was no proactive response to safety related information (‘competence’). The organisation did not appear to understand the regulatory effort, or show any signs of learning from its experiences (‘cognizance’).

Function types can also be classified as General Failure Types (302) – These can include issues such as poor operating procedures, communication failures and organisational failures – these can have a great impact in the prevailing conditions of the system. Having a culture of adequate communication and developing a co-operative environment where all members of an organisation are working towards a common goal are in part covered here. For example, in an organisation where there are deficiencies in the provision of a supportive infrastructure, an issue such as ‘inadequate training’ for staff members at this level can translate to a variety of ‘precursors of unsafe acts’ (184). The lack of a well established routine of procedures did mean that certain processes – such as the establishment of a database – took longer than anticipated, without the experiential knowledge, anticipation and planning of the sequence of activities (the establishment of a critical path) meant that there were considerable delays, and that set-up seemed chaotic. The core trials team were ‘detached’ from the other stakeholder groups – this meant that the conditions and culture that was developing in this team could continue unchecked, and attitudes towards rules and procedures were incompatible with ‘safety’ (186) – a culture that meant that when a number of events occur which should have put the organisation on

‘red alert’, it was not communicated to other parts of the organisations, and the core trials team did not seem to be aware of the importance of them.

Condition tokens include those psychological or situational states conducive to the commission of unsafe acts – these can include a high workload, an inappropriate perception of hazards, and ignorance of the system. When considering those factors that are related to knowledge/qualification (Information Processing Factors) it is important to consider that no matter how expert an individual is at coping with familiar problems, their performance will approximate that of a novice once their repertoire of rules is exhausted by a novel situation (38). Expertise consists of having a large stock of routines to cope with a variety of contingencies. In addition to this, there were a variety of stressors on the CI (Situational Factors) that made it a difficult environment in which to make decisions. The behaviour of the Chief Investigator did not obey group norms (Social and Motivational Factors) this led to an environment where staff felt demotivated, that trials teams did not feel supported, and the Trial Steering Committee did not feel they were in a position to advise.

All of these factors lead to there being a risk of unsafe acts. These can be classified as Mistakes, Slips and Lapses, or Violations – and are classes of error. Mistakes are planning failures, and can be defined as a mismatch between the prior intention and the intended consequences. For Slips and Lapses the discrepancy is between the intended actions and those that were actually executed, ‘failures of execution’ (38) – these are shown in the results through poor adherence to processes – leading to a chaotic environment and considerable delays. Examples of Mistakes in the results include both rule-based mistakes (through the application of bad rules)

and knowledge-based mistakes (which were a result of an inexperienced project management team).

Violations are defined as deliberate deviations from those processes that are deemed necessary to maintain the safe operations of a system (38) – the examples that are extracted here as part of the results are violations of ICH-GCP. Two factors are important in shaping routine violations, or habitual violations - a) the natural human tendency to take the path of least effort, and b) a relatively indifferent environment (i.e. one that rarely punishes violations or rewards observance) (38).

Table 17: Types and Tokens

TYPES	
Source types	
Commitment	<i>Organisation is motivated to observe regulations...:</i> "I don't think that [the Chief Investigator] had the best relationship with R&D and took criticism quite personally and was of the opinion of I'm going to do it my way" (Core project team member E3)
	<i>... but does not ensure resources allocated to attainment of safety goals</i> "The department as a whole was... a bit ill equipped to handle something so big... in a big hospital, there would have been a lot more expertise there to call from." (Core project team member E3) "It was more difficult than we thought. The level of project manager we wanted for the post just didn't apply..." (University staff member C3)
Competence	<i>The organisation's information system was inadequate.</i> "The delays in set up and initiation, were not appreciated-and then they were not acted upon sufficiently... By that time we were dealing with a mountain rather than a molehill." (University staff member C2)
	<i>There was no proactive response to safety related information.</i> "My understanding was that the project was struggling, but at no point was [the medical school] approached for advice or help" (University management H1)
Cognizance	<i>The organisation did not understand the regulatory effort...</i> "I guess people were assuming that [project managers and administrators] were working to deliver on that, and as it transpired they probably weren't." (University staff member C1)

... and had not yet learned lessons from related experiences

“The [sponsor] institutions, if they want to be successful, there’s a lot to learn - to be able to work better together you’ve got to have much better formalised structures much better awareness, and be prepared to support the staff that have achieved these awards.” (University staff member C1)

TYPES	
<i>Function types</i>	
Poor operating procedures	"Database development took a very long time to get completed. The database was being developed without the CRF, and then that the CRF was being developed and then the database was being modified and that's sort of inexperience, lack of planning..." (NHS trust employee B1)
Communication failures	"Everyone that was involved was detached, I only remember one management meeting, the whole of the time that we had the trial. I didn't even know that we had got the award, for maybe 3 to 6 months after, because [the Chief Investigator] didn't tell anybody." (Co-applicant G1)
Organisational failures	"I think it's a case of having the infrastructure in place to let the thing happen before you actually press the start button" (Trial Steering Committee member D1)
TOKENS	
<i>Condition tokens</i>	
Information processing factors	<i>The expertise of the chief investigator and study managers did not include "a large stock of appropriate routines to deal with a wide variety of contingencies"(38)</i> "[The Chief Investigator] ... gets the grants, and has the ideas, and his expertise is there... but he is not as good at managing" (University management H1) "A lot of the time I was making things up as I went along. I think that if this study was run somewhere else, I don't think I would have even got a sniff, I don't think I'd have even got an interview... I think that our lack of experience made things impossible" (Core Trials team member E3)
Situational factors	<i>The "ergonomic quality"(38)pp58-59) of the human-system interface was poor – with changing management structures within the higher education institution (HEI), incomplete integration between the higher education institution and an NHS trust, and inadequate research infrastructure across the piece. The Chef Investigator's workload was high.</i> "At the time... the relationship between [The University Department and The Medical School] was unsure. [The Chief Investigator] had a lot on his plate, and there were issues with [The Chief Investigator] and

	the NHS trust, with regards to money management, which added to his feeling of being unsupported.” (University management H1)
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Table 17 (cont)

TOKENS	
<i>Condition tokens</i>	
Social and Motivational Factors	<i>The Chief Investigator's behaviour did not fit with group norms and the project team was demotivated.</i> “We expect CIs to make the decisions... but not to manage and micromanage to the level that was happening. It does hinder the decision making. It creates another layer of escalation on every issue that's required on the level of the Trust and on the university side. We couldn't go back and say, we'll replace the CI” (NHS Trust employee B1) “I think (within the trials team) the major problem was the feeling of hopelessness - and the how can we do this. What it needed was a bit of management” (University staff member C2) <i>Members from external sites also did not feel supported from the central trials team – the trial did not seem to be a priority</i> “There was creep and there was delay and not enough urgency. The numbers in any study, if it's 2000, that's the power of the study and it doesn't matter in any study, you have to power it accordingly, but this didn't come across as a massive priority from (Central Trials Team), and I think that's one of the problems.” (Staff from external site I1) “My work, predominantly, is that of a clinician. I am interested in research, and do try to get involved in projects that interest me, or that I feel might help colleagues and answer important questions of patient treatment. What I have found is that research is very expensive, and involves a great deal of investment and commitment, but that the rewards are not always immediately apparent. The money that is awarded to a particular trust or institution for undertaking a research project is rarely seen by the clinician involved, or their department, which makes it more difficult for consultants to find the time, or the motivation to take part in clinical research, or participate as a contributing centre as part of a multicentre drug study for example” (Staff from external site G2) <i>Members of staff that worked closely within the trials team did not feel listened to – especially by the Chief</i>

	<i>Investigator, as when they raised questions, they did not feel listened to, or that their opinion was valued</i> “If you raise your first query, and you get met with a barrage of, 'well, why are you doing this' and, 'we're not going to do that' and 'its pointless' and 'what's the point of it' and then that means that next time you come up with an issue you're, like, well, I cant raise this issue now, and, well, human nature is that - oh, well, we'll leave that then, we'll leave that issue, and, it might not surface again. And it'll get buried, and invariably it resurfaces and becomes an issue again. But much later in the process. And there's more anxiety and then there's just this thing of - it isn't worth the hassle. So everyone, you know, the whole morale just goes down, both from the study team that are trying to run it, and the sponsors and the university that are involved.” (NHS Trust Employee B1) <i>The Chief Investigator had been involved in a number of trials before, and was seen as experienced – a member of the trial steering committee suggested that his experience meant that less experienced people were not in a position to advise</i> “I mean, I'm not one to tell (Chief Investigator) to do anything in terms of running a clinical trial. I think it's a crying shame that this has happened to the trial.” (Trial Steering Committee Member D4) <i>The communication between the Chief Investigator and all stakeholder groups was poor – from the point of view of this member of the trial steering committee, there was little opportunity for involvement, or to discuss the trial design at all</i> “With the steering committee, I mean you must have seen the Charter - it's meant to provide an independently chaired body which reassures the sponsor and the (funder), that the trial is being done properly and we were sort of in a backwards situation, where (Chief Investigator) had written a protocol and submitted it to (Ethics), had almost started before we had our first trial steering committee meeting” (Trial Steering Committee Member D1)
TOKENS	
<i>Unsafe act tokens</i>	
Slips and lapses (execution failures related to attention and memory)	“Now I think there was a failure of management when we had gotten a large number of people in and the continuation of data was coming. So a paper system

respectively)[1, 2] <i>The trials team were inexperienced, and a number of processes that were necessary – such as the inclusion of new trials sites, and careful checking of CRFs and data processing – took longer than planned due to poor adherence to processes, leading to significant delays</i>	should have been put into place to start the data acquisition rather than wait on the database that went through numerous alterations, and took an extraordinary length of time" (University staff member C2) "I think the sites, there are so many of them and the SSI forms were nowhere near being complete, I think that probably could have been handled better. I mean there were so many. I think that was the problem. We just needed to set up sites as quickly as possible and it was chaotic." (Project team member E3) "There was (Project manager) in first, he had a breakdown. This wasn't transmitted or made clear to the (Funding body) Perhaps the whole project should have been suspended until something was done, but the clock continued to run, so it looked like we were entirely flat-lining, which of course we were in terms of numbers, and that's because there was nobody doing anything" (University staff member H2)
Mistakes (planning and problem-solving failures)[1] <i>Rule-based mistakes, through the application of bad rules (e.g. the hypothesis that changing diagnostic criteria would improve on previously observed rates, and delays in site inclusion because of the need for periodic reapplication for ethical permissions) and knowledge-based mistakes (inadequate trial planning and implementation content expertise) were observed.</i>	"At study start there were far too few centres or practices anywhere near start-up and a hugely optimistic recruitment target was agreed with the funding body." (Trial Steering Committee member D5) "Every time you need to go to add a new site in a clinical trial, that's a major amendment and has to go through the ethics committee. We held back with enrolling new centres until there was a large enough number of centres raring to go and trying to get them all enrolled at the same time" (Project team member E3) "We had issues around the database. We were kind of new to this.. and kind of oblivious of what the real costs were - I think we built in about, 20 - 30 thousand pounds worth of costs for the database development, and when it actually came to fruition we were actually looking at a bill of about 68 thousand so triple what we predicted for the costs" (University staff member C1)
Violation (deliberate deviations from those practices that are deemed necessary to maintain the safe operation of a	<i>Violations of ICH-GCP include:</i> <i>8.0 Essential documents for the conduct of a clinical trial</i> <i>4.9.7 Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should</i>

potentially hazardous system) <i>Two factors appear to be important in shaping habitual violations: the natural human tendency to take the path of least effort, and a relatively indifferent environment (i.e. one that rarely punishes violations or rewards observance)(38). An external review that was commissioned by the sponsor (university) organisation highlights a number of safety violations, and comments specifically on the culture and environment of indifference.</i>	<i>make available for direct access all requested trial-related records.</i> <i>4.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.</i> <i>4.2.3 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.</i> <i>5.1.4 Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.</i> <i>4.10.2 The investigator should promptly provide written reports to the sponsor, the IRB/IEC and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.</i> “The reviewer is not convinced that the current staff, who are inexperienced in setting up and running CTIMPs, fully understand the volume of work which still has to be done, or how to do it in a timely, efficient manner, the reviewer has concerns over the willingness of the trial team to accept the intervention and advice from an external CTU” “Other serious problems which were noted by the reviewer included poor adherence to the principles of GCP, the most serious example of this is the disappearance of the trial master file (TMF) which seems to have been taken home by the previous project manager and has not been seen since. The reviewer was shocked to see the casual acceptance of this extremely serious situation and feels it indicates a lack of understanding of the principles of GCP and the purpose behind them” “Of the CVs reviewed, only the Chief Investigator has GCP training listed” “Reliance on a single member of staff – The current project manager is in an isolated position with no other senior member of staff available for cover or support, apart from the CI, who sees his role as science rather than the day-to-day running of the trial set up” “Key pieces of work, such as the development of the database are not covered by an official contract, and terms and conditions had not been defined.” (External review of trial progress commissioned by sponsor University)
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	“We tried to find accommodation and it was higher in cost than what we had planned for, so we scrambled around for any kind of accommodation, and we got to the point where the then project manager was then looking at rooms above a pub. In the end we had the project managers working out of a hotel room” (University staff member C1) <i>Inexperienced project managers</i> "It then got very much put on us as a sponsor to be the experience to drive the study, Because (Project managers) were brought in to be a stop gap really, until they got any experienced project managers. But they had no prior experience of running a clinical trial not even a single centre study" (NHS Trust employee B2) <i>Loss of expertise when co-applicants withdrew their support from the trial</i> "Major problem of course of which arose, was that some of the co-applicants and the trials unit pulling out quite early in the project. Certainly that would not have helped - there was no one to share certain items of the burden with." (University staff member E3)
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Figure 27 shows how multiple layers of defence within the organization were gradually permeated through a series of failures. In brief, poor commitment and cognizance at the top of the organization (source types) allowed poor operating procedures, organization and communication (function types). Critical among these was the permission for the investigator to run a high-risk study, first with minimal and then with no CTU support. As a result, the study was in the hands of people with no stock of routines to address the contingencies which arise during the planning and implementation of large-scale projects, further aggravated by ongoing organizational change and poor team management (condition tokens). The resulting mistakes, lapses and violations lead to avoidable delays in regulatory approvals, late initiation of sites, failing to recruit participants to time or target and the closure of the study by the funder. Had the study not closed at that point it would have undoubtedly been closed by the MHRA due to two serious breaches of ICH GCP at the next inspection.

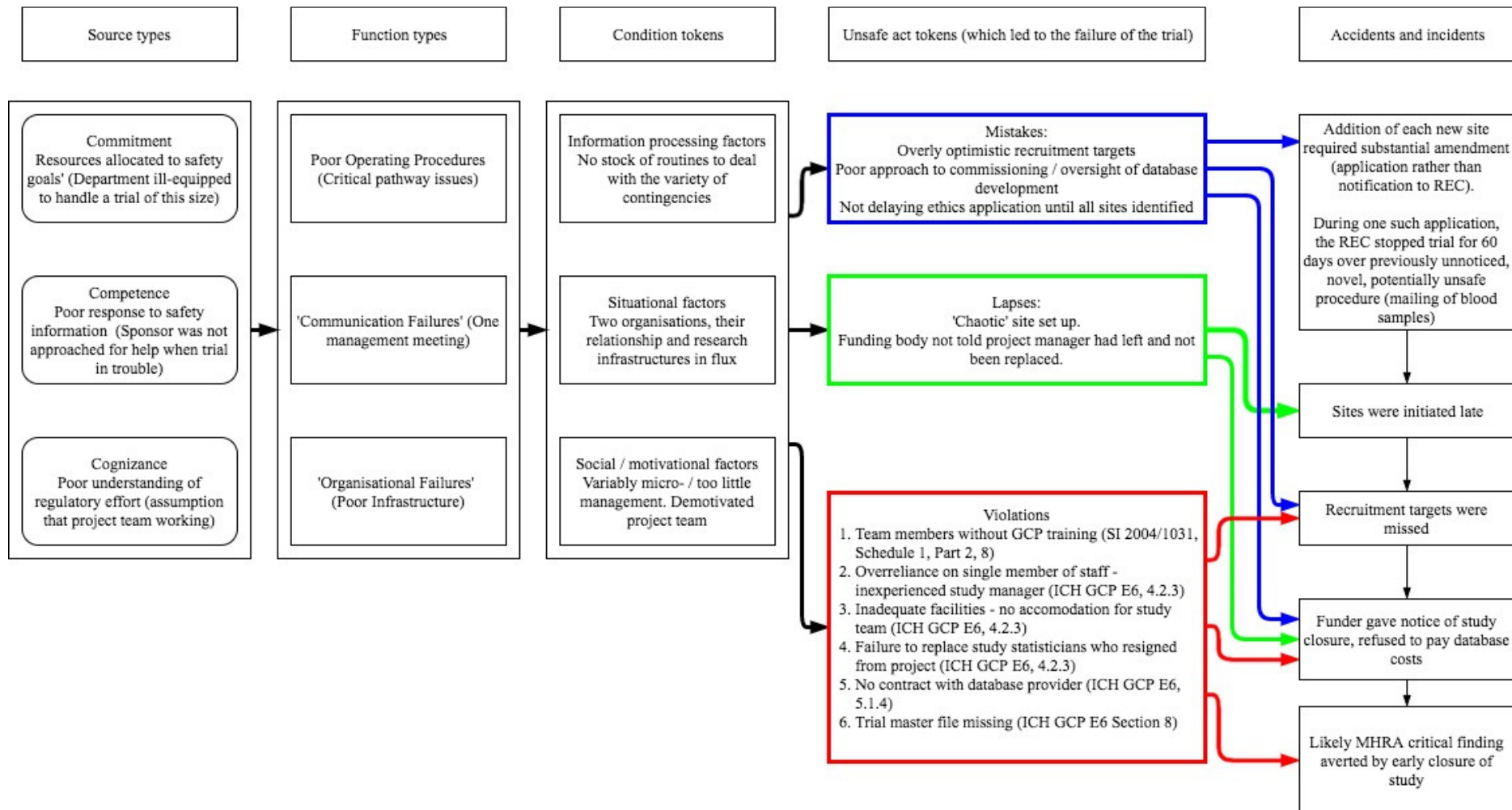


Figure 27– Results (38) Based on Human Error by J Reason

7.5.2 Mistakes and lapses classified in the team errors taxonomy

Table 18 shows a distribution of responsibility for errors. As described in ‘Figure 20 Team Error Process’ Human error can be classified into Slips, Lapses and Mistakes. Mistakes and Lapses occur during the planning and thinking process, whereas Slips primarily occur through the execution of a task. As Slips are actions in the action process of an individual, whereas Mistakes and Lapses are more likely to be due to a group process – it is these events that are pulled from the results described as part of Table 17 and Figure 27 that are used in the taxonomy of team errors described in the table below (39).

Team Errors – applied to the case study

Mistakes (p227)	The hypothesis that changing diagnostic criteria would improve on previously observed recruitment rates.	Individual Independent Error (CI) Failure to Detect
	Delays in site inclusion because of the need for periodic reapplication for ethical permissions	Shared Independent Error Failure to Correct
	Inadequate trial planning and implementation content expertise (late delivery and overspend relating to database)	Shared Independent Error Failure to Correct
Lapses (p244)	Poor adherence to processes, leading to significant delays (chaotic site set-up)	Shared Independent Error Failure to Indicate
	No communication with funding body regarding the loss of project manager	Individual Independent Error (CI) Failure to Indicate

Table 18: Team errors

Deficiencies in communication are something that has been suggested as a shortcoming in this trial by a number of individuals that represent a number of stakeholder groups that were involved in this study. These deficiencies in communication are a crucial contributing factor to these 'Failures to detect' errors. These often arise from 'excessive belief', 'excessive professional courtesy' and 'over-trust' (39) in those that the rest of the team feel 'know best'. This 'Excessive Authority Gradient' can severely impair effective error detection, and may be a contributing factor as to why these issues were not noted, and once they were noted, were not acted upon.

8. Discussion

"The interactional complexity of modern systems means that component-level and single causes are insufficient explanations for failure." (303)

8.1 Summary of Main Findings

In my literature review in Chapter 2, I demonstrated factors associated with poor recruitment to RCTs including those relating to study design, clinician and participant factors and the research environment. In Chapter 4 two context-specific conceptual frameworks, were introduced - ICH-GCP and Robinson's Risk Management framework; I also reviewed Reason's model of organisational accidents to understand how potential sources of failure could be classified and how they interact.

The case study trial (Chapters 3 and 7) showed several of the factors that lead to failure. It had shortcomings in its design or 'definition' phase which were overlooked by the trial team, funding body and sponsor organisations. In the 'planning' phase, the team's relationship with a CTU and two co-applicants collapsed, there were delays in appointing a local project manager, finding team accommodation, and commissioning a study database. The study fell behind time, there was budgetary overspend, poor observance of ICH-GCP, staff dissatisfaction, and minimal communication with stakeholders beyond the core team. During the 'implementation' phase serious breaches of ICH-GCP (missing Trial Master File, frequent absence of GCP training records for recruiting staff); and ultimately failure to recruit to time and target lead to the funder closing the study before an MHRA

inspection resulted in the same outcome and considerably greater reputational damage to the organisation.

Many of the mistakes and lapses were shared rather than individual; all were avoidable, but the combination of inadequate resourcing and experience, together with the motivational problems arising from these and other factors, created an atmosphere in which mistakes were not identified or were identified and not corrected due to an 'excessive authority gradient'.

8.2 Research findings in context of the literature

The methods used in the analysis were quite different to those employed in previous studies of trial failure which I described in my literature review. Although in the initial analysis of the results inductive methods were used – when the data were revisited, the framework I used had themes that were grounded in social science literature so that individual failures were not overly focussed upon, instead I looked at them at an organisational level.

I used a single case study design, approaching issues from an organisational perspective, using a framework with themes that had been derived from the literature was an innovative approach. The methods chosen, in context of the literature are discussed at length below, under the section for the strengths and weaknesses of the study.

As a result of the analysis of this case study, a number of areas have been identified where there were shortcomings in the definition, planning and implementation phases. My literature review found (figure 4, chapter 2) several key themes that

previous studies had identified as contributors to successful participant recruitment. These included factors relating to study design, such as the acceptability of the intervention, ensuring participant availability and reasonable inclusion and exclusion criteria. Feasibility and pilot studies are seen as a way of taking reasonable precautions to test a study and associated processes in order to prevent issues with study design affecting recruitment. However no formal feasibility studies or pilot phase took place in this case study trial.

One of the core findings from the literature review was the importance of research infrastructure, such as a Clinical Trials Unit, or similar, with a stock of experience and techniques so that negotiating bureaucracy and the recruitment of trained staff to a project is made much easier. This is reflected in the results of the case study analysis here – in that there was a lack of experience, meaning there was not a “large stock of appropriate routines to deal with a variety of contingencies” (pp240). A system of governance that is well maintained to ensure research quality, and the maintenance of an open culture with good communication between stakeholder groups is an important feature of maintaining a safe research infrastructure – this could be introduced through the establishment of ‘feedback loops’, a concept that is discussed in greater detail later on in this chapter.

The choice of sites, and then being “Research Ready” was a factor that was also explored as part of the literature review (pp73). In the case study, the large number of sites that needed to be recruited meant that the trials team did not have the luxury of being selective over the centres that were involved. (pp215) which meant that it

took more time and effort to involve sites, and those that were included were not necessarily in a position to recruit the required number of participants.

8.3 Meaning of the research and implications for research stakeholders

8.3.1 Overview

The key messages of this work are that: (1) that human factors are a threat to the sound definition and planning of a research project; (2) responsibility for the success of a research project should be seen as distributed, rather than vested in an individual; (3) the presence of authority gradients hinders the identification and correction of slips, lapses and errors. The development of feedback loops and a senior management culture of rapid response can provide defences against the types of poor outcomes described in this case study.

In the following sections key areas identified as part of this study, linked to the failure of the trial or increased risk are discussed in turn, along with ways of mitigating these risks, managing them, and potentially reducing risk.

Table 19 – Approach to managing risk

Section	Key area of risk	Approach to managing risk
8.3.2	Definition Risk >> Agreement to unrealistic participant recruitment targets	• Appreciation of the planning fallacy, optimism bias, reference class forecasting
8.3.3	Planning risk>> Provision of suitable Chief Investigator	• The role of the individual within an organisation
8.3.4	Failure to detect errors within the organisation	• Culture within an organisation • The danger of authority gradients • The importance of safety feedback loops
8.3.5	Investigation of adverse events or accidents/breaches relating to a trial	• What happens when things go wrong • Systems approaches rather than root cause analysis

8.3.2 Optimism and the setting of recruitment targets

At the definition or planning phase of the case study trial, unrealistic targets for participant recruitment were set. As discussed earlier in the thesis, this could reflect an inexperienced recruitment team. This was also an emergent theme highlighted in the literature review, and showed links between recruiter inexperience and the prevention of participant recruitment.

The planning fallacy, optimism bias and reference class forecasting

Key errors in the definition and planning stages involved what psychologists refer to as the planning fallacy, in which managers make decisions based on “delusional optimism rather than on a rational weighing up of gains, losses, and probabilities”.(304) (305) (306, 307) Projections of costs, demand, and other impacts of plans are frequently inaccurate explained due to optimism bias – in which benefits are overestimated, costs underestimated – and strategic misrepresentation. As in my case study, initiatives founded on such a basis are unlikely to deliver the anticipated returns on budget or on time. The best defence is the use of reference class

forecasting - using available data from similar situations to help predict what might happen in a project (308). Scholars have made the case for better reference class forecasting in the definition and planning of RCTs for over forty years(278), but there is little evidence that it is consistently adequately conducted. (18, 90)

8.3.3 The role of Chief Investigator

As described before, the Chief Investigator of a trial takes overall responsibility for the design, conduct and reporting of a study. In the case of this trial, a number of threats were related to the behaviour and conduct of the trial Chief Investigator – including their previous experience and competence to take on the role of managing a clinical trial. Here we discuss the role of an individual within an organization, and whether replacing a key individual would be enough to mitigate all potential risk.

The role of the individual within an organisation

There have been reports that when organisations use a ‘Systems based approach’ to address an issue with regards to a mistake, or adverse event, it is ‘all too easy’ for individuals to ‘blame the system’ rather than taking any personal responsibility for the adverse event that has occurred. (309) James Reason (310) asked whether safety specialists can ‘cast the net too widely’ by looking at possible error and accident contributions widely separated in both time and place from the error itself, rather than focusing on the individual at the human-system interface. Wachter and Pronovost suggest that there needs to be a balance between ‘no blame’ and individual accountability in a healthcare setting, describing the need for a more aggressive approach for poorly performing (practitioners). (311) This emerged from analysis of a system that had done ‘all that it could do’ and despite this, that the

individual practitioners still managed to ‘mess things up’ (309). So when the system has done all that it can where can one go – how does one address the personal accountability of the individual? Shojania and Dixon-Woods describe how the field of patient safety could not have reached the traction that it has without first identifying and correcting the systems issues, but that now it is important to focus on the performance and behaviours of individuals within the healthcare organisation (312) particularly those individuals that display incompetent or grossly negligent behaviours. (313)

A balance is needed. There is very little to be gained in sanctioning an individual who has the potential to contribute valuable information that could benefit the whole organization(309). In order to understand the cause of adverse events, the likelihood of them happening again, and the impact of potential remedial efforts to prevent their future occurrence, there must be focus on those individuals involved in order to understand their perspective and experiences, as discounting these people and not working collaboratively with them potentially severely limits the potential for learning from an adverse event (310, 314).

The best way of promoting an organizational culture with safety at its core is to have a culture that allows the leaders of the organization to hear bad news. A culture that is alert to the potential fallibility of the system, has the potential to individuals to account, but also to promote a climate which allows individuals to report freely if they have any concerns.

8.3.4 Failure to detect errors within an organization

The first step to recover from errors is to detect their occurrence. If a team within an organization does not notice errors there is no chance to be able to correct them (39). In the case of this trial, members of the steering committee and members within the sponsor organisations felt unable to challenge the Chief Investigator. The work of Sasou and Reason (1999) describe links between errors and performance shaping factors, such as excessive authority gradient, excessive professional courtesy and poor communication (39), leading to an organizational culture that is less open, and an increased risk of error. Improved error detection can be addressed by giving consideration to the culture within an organization, addressing the presence of excessive authority gradients and considering the introduction of safety feedback loops – all of which will be discussed below.

Culture within an organization

There is an increasing emphasis based on the importance of understanding the shared attitudes, beliefs, values and assumptions that underlie how people perceive and act upon issues of safety within their organisations (315). These shared characteristics are referred to the ‘safety culture’ of an organization (316). This can have an impact on the design of tasks and processes, the way that teams interact and communicate with each other, and how members within a team are trained to participate in a safety culture (42) and how concerns about safety are acted upon.

There are two clear but competing concepts around organizational culture – the school of thought that regards culture that something which an organization is (a descriptive metaphor, and an aspect of an organization that cannot be changed) and

those that conceive of culture as something that an organization has (a variable that can be manipulated, measured, and most importantly, influenced or changed) (317). This distinction is important because if culture is something that an organization has, then it might be possible to change and manage it in the pursuit of new objectives and shaping new approaches.

Organisational culture can be a target for change, and is essential in order to make the necessary cultural change towards openness and accountability. This is a culture where reporting of mistakes, including near misses, is routine, and demonstrations of learning from mistakes are behaviours that are clearly valued and rewarded (318). Michael (1976) suggested that embracing error is feasible in organizations that recognize and reward these behaviours, and the view that error is indicative of incompetence leads people in organizational hierarchies to systematically suppress mistakes and deny responsibility (319). As long as the acceptance of responsibility at managerial levels is seen to be taken seriously, this will help to negate an authoritarian “top down” culture. Just as importantly, this sharing of responsibility across all levels of an organisation should allow learning to occur more readily and more appropriately (320, 321)

The danger of authority gradients

High Reliability Organisations (HROs) such as nuclear power plants and the aviation industry have come to understand that authority hierarchies do not usually correspond with knowledge hierarchies; (322) regular communication and feedback from frontline workers is required for errors to be identified and resolved (171, 323).

On the other hand, healthcare organisations and higher education institutions are often subject to entrenched hierarchies and organisational gradients (324).

Developing a ‘culture of safety’, in which staff feel comfortable reporting problems without fear of retribution is essential for good decision making (325). Developing a culture of safety is challenging in a complex, emergent system, with professional fragmentation, diffuse accountability, hierarchical structures and strong traditions of individualism (326), but exemplars are known, for instance in surgical settings. (322, 327)

The importance of safety feedback loops

Reason’s proposal for ensuring the control of safe operations, involves: (1) the establishment of a sensitive multichannel system for feeding back information about function types and tokens to an organisation’s senior management (Figure 28); and, (2) their commitment to respond rapidly to actual or anticipated changes in the safety realm (38, 186).

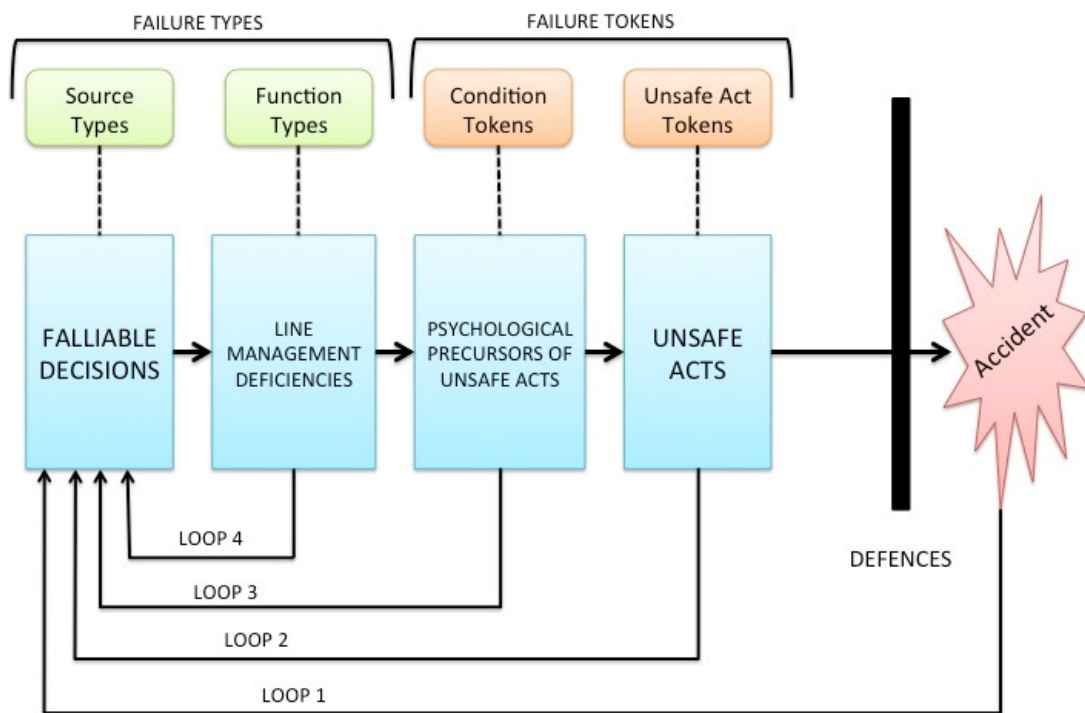


Figure 28– Feedback loops (38)

An example of Loop 1, the reporting of an accident, was observed in this case study; sponsor representatives were alerted to the threat of closure, served by the funder due to lack of progress, after which the Chief Investigator was replaced to try to prevent trial closure. Reason characterizes such acts ‘local repairs’ and that, as in this case, the information supplied in Loop 1 is usually too little and too late for any effective control or remedial action.

In a well-functioning trial, internal auditing and discussion of unsafe acts (e.g. GCP violations; see Figure 27), with feedback of safety information to higher levels of the organization where necessary, are characteristic of Loop 2. This loop relies on trial

management groups to self-police, given minimal, largely hands-off supervision by R&D offices and bi-annual inspections by the MHRA; it cannot be relied upon where excessive authority gradients exist. Whilst the responsibilities of CTUs do not extend beyond Loop 2, they do make its use more reliable, as CTU-specific MHRA inspections incentivise CTU staff to report uncorrected violations to the sponsor, thereby holding the Chief Investigator to account. Staff who are directly line managed by Chief Investigators have no such incentive. In other words, Loop 2 is fragile in the absence of CTU.

It is Loops 3 and 4 that Reason recommends as particularly important in the prevention of accidents, but which were wholly absent in our case study trial. The effect of condition tokens (the incompetence of the investigator, organisational change and socio-motivational team dynamics; see Figure 27) were either unappreciated or discounted by senior management. Arguably, there are few incentives for public sector organisations in constant flux with diminishing resources to monitor and challenge those willing to lead research, while there is every incentive to gamble on their suitability, given the prestige and resource associated with grant income.

Loop 4 involves reporting weaknesses associated with function types (poor operating procedures, communication failures and infrastructure; see Figure 27) back to senior management. Outside of High Reliability Organisations, it is rarely politically expedient to report such weaknesses. However, once again, full involvement of CTUs can mitigate against the need for such a feedback loop, because their core

function is to provide a stock of routines and systems, a pool of experience that outlives individual trials and members of staff.

Feedback without rapid and effective response does not enhance an organisation's degree of safety (38). A general indicator of an organisation's safety functioning is whether this response to safety-related data involves denial, repair or reform (38), pp211. In our case study, the Chief Investigator was largely in denial, not through suppression (punishment or dismissal of those who report breaches, and removal of their observations from the record), but through encapsulation behaviour (disputing or denying the validity of safety-related observations)(38). This was principally through the marginalisation of concerns and blaming external factors for failures (pp 227). Repair actions were late and limited (replacement of the CI), with the wider implications were largely denied. Three years later, when I started writing this up, the organisations involved were still discussing certain reform actions to prevent recurrence of a similar trial failure.

There are no simple solutions to organizational problems. Healthy organisations are characterized by their commitment to continuous self-assessment and reform. The introduction of new procedures would be an example of an effective reform action – Procedures comprise the accumulated craft wisdom and practical knowledge of the organization, and good procedures should tell people the most efficient and safe way of completing a task. The introduction of standard procedures and a culture where their use is encouraged would potentially prevent future error and violations.

8.3.5 Investigation of adverse events or accidents/breaches relating to a trial

If an error is detected, or the potential danger of an adverse event, a team can then take action to address this error to prevent it happening again. There will also be incidences of adverse events occurrence and a requirement for post-hoc analysis. In the following section, discussion of individual behaviours when things go wrong – particularly in an organization with excessive authority gradient is discussed.

What happens when things go wrong

It is important to understand how individuals – especially at team-based or management level - approach and deal with adverse events, as this may help understanding when it comes to trying to reduce the risk of error within an organization. What happens when things go wrong, and when mistakes are made? Marilyn Rosenthal (1999) gathered data in the field of patient safety, looking at more than 200 cases of medical near-misses or adverse events due to medical error. She found that in all cases it took months or even years before physician colleagues took effective action against errors that they had witnessed, or dangerous practice that was of concern to them (328) It illustrated the danger of working in a culture of blame. Rosenthal describes, rather than a conspiracy of silence, the dominant reaction that of uncertainty, denial and ineffective intervention that stem from a shared personal vulnerability, that which she describes as “There go I but for the grace of God’ (329). There have been descriptions of the ‘Culture of Hiding Errors’ in medicine, that is thought to stem from a professional tribalism, (330) which echoed in the work of Atul Gawande (331).

The role of the chief investigator of a large clinical trial is prestigious; they may be expected to function without error. Chief investigators occupy their role largely because they are experts in their field, specialists, and authorities, and not expected to err (332). If an authority does make a mistake, this pressure to be infallible can create a strong pressure to dishonesty (333) and to cover up mistakes rather to admit them in the hope that this will not lead to censure, or their colleagues to think that they may be incompetent.

Historically it has been observed that organizational norms of this nature may perpetuate these behaviours within medical and hospital practice, and in the clinical literature it has been noted that these attitudes and patterns of communication can have an adverse impact on patient care (334, 335). The presence of authority gradient or hierarchy, has been linked to communication breakdown within high-pressure clinical situations (336). This can be linked to a hesitancy by team members to challenge an incorrect decision by a perceived superior (337). Work environments that encourage 'speaking up' by all members of the team encourage learning and a team approach to patient safety in an effort to reduce the incidence of adverse or undesirable outcome (338).

Leadership behaviour can affect how errors are handled within an organization. A highly authoritarian environment can be associated with a culture of suppression of error (318). Working within a pressured environment within an organization is extremely demanding. The chief investigator was in a position of power, but also had colleagues around him in the form of the Trial Steering Committee who were similarly qualified and had a similar background. All recognized the pressure that he

was experiencing, but did not feel able to raise any concerns at a level where any behaviour could have been challenged or addressed. This results in the profession clubbing together to provide support and maintain the norm of non-criticism .

Systems approaches rather than root cause analysis

Incident analysis in the aftermath of an adverse event is intended to identify the factors contributing to the genesis of a particular adverse event. Often, approaches to simple root cause analysis result in a simple linear narrative that displaces more complex accounts of multiple and interactional contributions of how events really unfold (339). In our case study, the salient features are classic failures of middle management identified by employees, failures of organisational performance, communication skills, relationships with others and personal characteristics (340). It would be easy to isolate the chief investigator as the root cause of the project failure. However, this would be misleading and does not allow for the complex underlying reasons to be explored and identified. The use of social science theory and ICH GCP yields more than a simplistic explanation. Informants often praise or blame individuals without considering the bureaucratic restraints they are subject to (341), or a more general lack of teamworking culture in an organisation (342). One of the core principles of ICH-GCP (37) is everyone has responsibility for flagging breaches, and all members of a team should feel empowered to report any concerns, and part of the sponsor's responsibility is to monitor the investigator.

8.4 Strengths and Weaknesses of Study

This study was a single case-study design, with merging and triangulation of data from two sources, that of interview data, and documents relating to the clinical trial

under examination. The data were used in order to help and understand why the trial failed to progress, why it failed to recruit and the factors that contributed to its eventual closure. Within-case analysis involved the use of the Framework Method of Analysis of the qualitative data. The use of case study methodology together with social science theory brings structure and enables causal pathways to be identified (204).

Single, unique case study

The use of a single, unique case study enables researchers to examine on a deeper level, the reasons why something happens, and allows the recognition of factors such as the social structure of an organisation, how mistakes can be systemic and socially organised, and built into the nature of professions, and organisational structures – discussed in the report by Vaughan (125) which looked into the crash of the ‘Challenger’ spacecraft at NASA – this ‘Sociology of a Mistake’ is similar in principle to my case study (124).

However, potential problems can occur with a holistic design; there is a risk that the entire case study may be conducted at an abstract level – lacking the clear measures or data needed – a potential pitfall when a single case study in unique circumstances is considered – this is described in Yin (2003) (204). Another issue is that the entire nature of the study question may need to be revised – a planned study question and methodological orientation may need to be revisited as the case study proceeds - Yin (204) uses ‘propositions’ to guide the research process, whereas Stake (1995)(343) applies what he calls ‘issues’ to help guide the research and aid the development of concepts(220, 344). Some people claim this flexibility as strength of case study

design, and others describe this shift in which the implemented research design is no longer appropriate to address the research questions being asked, an inherent weakness (204).

Personal involvement

Through my original involvement in the case study trial as clinical researcher, I already had a degree of rapport with a number of individuals that were involved in the trial – particularly those working as part of the local project team, and within the sponsor organisations. It is possible that, as the interviewer, that I was not as challenging to interviewees – particularly as a number of them were more senior colleagues and were working in the same field. There are advantages and disadvantages to working and studying settings where peers are involved, and this is discussed in the literature (222, 240). Although the researcher may benefit from an understanding of the setting (345), a greater degree of familiarity with the individuals being interviewed (346), and the issues being discussed, this relationship may have affected the interviewer-interviewee dynamic. The topic guide I used meant that all questions were asked to all participants in a similar manner. When it comes to interpreting the findings however, it is possible that a greater familiarity with the subject, and having the perspective of ‘experiencing the conditions’ that the interviewees are describing helped with interpretation of the findings and made them more meaningful (90).

Case study methodology has its roots, and derives from participant observation, with the first generation of case studies being published having ‘participant observation’ as the principal method of data collection (347). The participant observer gathers

data by participating in the daily life of the group or organization being studied (348). Participant observation is not without its problems, involvement with the observed participants can impact the observer's point of view (349, 350). My immersion in the study setting, and personal interaction with the study participants does risk the blurring of the boundaries between researcher and interviewee – particularly when the subject is of a sensitive or personal nature (351, 352). In this research, I engaged in dialogue with individuals about their experience, often exploring opinions that had not been voiced before. In my role as a participant observer, interviewees may have felt more comfortable in sharing their experience with me when they felt rapport, confidence and trust (353).

Use of Root Cause Analysis

I used the '5 Whys' tool (257) to inform the structure of questions used for the interviews, as that is the most commonly used tools and approaches to Root Cause Analysis in healthcare. This seemed, in the early parts of my research journey, to be a good approach - and a way of 'drilling down' to find the single root cause of any issue. This has been one of the criticisms of using this tool in healthcare – it forces users down a single analytical pathway for any given problem (32). I developed an understanding that trial was being undertaken within the context of a complex system – and the failure of the trial also had a systemic basis. After obtaining the interviews, I could appreciate that the use of the '5 Whys' tool meant that there was a greater depth of information elicited. The use of a theoretical framework that encouraged analysis of the issues on a systemic level allowed a greater breadth of understanding of this complex problem.

Limitations with the use of the '5 Whys' tool have been documented in the literature, including the acknowledgement that classic RCA is not based on any specific theory of human error or system failure (151). An RCA typically focuses on 'what' happened and 'who' was responsible, rather than identifying 'why' an event occurred, which can facilitate a culture of blame. In addition, on occasion there is the risk that the root causes identified in an RCA are nebulous and not-actionable, for example 'poor communication' – which often requires an understanding of the behaviours and system issues that lead to breakdowns of communication (354) it also places the focus on a single root cause as the target for solutions, and assumes that the most distal link on the pathway (the 5th 'why') is where the focus and intervention needs to be placed (32).

One of the main problems encountered with RCA and its application to healthcare is that there is a risk that feedback processes fail to be established or maintained. Peerally et al (339) discuss this, reporting an example of an untoward incident that took place, subsequent root cause analysis, introduction of a new protocol, and a year later in the same hospital, the same untoward incident happened again. The authors discuss that feedback mechanisms in healthcare RCAs function poorly, and contribute to the disenchantment of staff (355, 356), in part due to poor reporting of the RCA outcome to those involved in the untoward event, disseminating findings (357) and making recommendations simple and actionable. Learning from the analysis of an event is essential, and Ramanujam et al (358) recommend that an important action following completion of an RCA would be for a team to develop an informed set of strategies to learn from event analysis. The approach to post-event analysis is discussed later in this chapter. The establishment of feedback loops would

promote a professional, proactive and responsive organizational culture, cognizant to risk and able to respond appropriately to threats.

RCAs in healthcare organisations often fail to explore deep system problems that contributed to safety events (359), Consequently, corrective actions focus on changing human behaviour rather than system-based changes (360). My analysis, focuses on an organisational system based approach instead.

James Reason characterised the goal of error investigations as draining the swamp not swatting mosquitoes (38) Too often, RCA teams focus on the first causal factor identified (eg, staff violation of the allergy-checking policy) rather than considering such factors holistically as parts of a sociotechnical system (ie, interactions between people and technology embedded in an organisational structure) (361).

The point of RCAs lies in surfacing deep system problems - these are the problems that are most difficult to recognise and to solve. The ideal outcome here would be to drain the swamp of latent conditions and not swat at the mosquitoes of superficial active errors. Yet, draining swamps is extremely difficult, involves extensive resources and extensive restructuring of entrenched structures – the outcomes following the completion of a root cause analysis do have the risk of being idealistic, fantastical even, and may be difficult to find practical and workable solutions for. Rather than radical restructuring of how organisations work, undertake a review of behaviours within a hierarchical system and addressing organisational culture, as Trbovich et al suggest, “In the absence of greater investment in and support for

RCAs, continued swatting at mosquitoes with education, reminders and new policies may well be all we can expect.” (361)

Reason's theoretical framework

Theory offers a systematic way of understanding events, behaviours and situations.

A theory is a set of interrelated concepts, definitions, and propositions that can be used to explain or predict events or situations by specifying relationships among variables. The main thrust of this study has been to examine failures that have occurred and to try and identify a range of factors (particularly organisational) that may have contributed, rather than just focusing on individual failures that had occurred.

The use of Reason's theoretical framework (38) to order the empirical data helps to highlight that what happened in this study is not a 'Black Swan' or random event. Rather, the potential for catastrophic project failure is inherent in human nature and in the conflicting incentives at work within organisations. Post-event project evaluations provide a basis for continual quality improvement in other projects and at other units.

Research papers that have discussed trial failure tended to be purely empirical – discussing more individual 'lessons learned' that give anecdotal accounts of single trials, often from the viewpoint of the chief investigator (23, 97, 362). My aim was that through the application of social sciences theory, and the understanding of problems as systemic, that these organisational factors can be taken into greater consideration when planning a clinical trial.

It is challenging to attempt to view a problem at an organisational level – without a systems approach it may be relatively straightforward to identify a single cause for failure. Managing and anticipating risk in this way can lead to underestimation of the irregularities that an organisation is likely to encounter in the future. Reason (38) explains that Causal analysis is influenced by representativeness and availability heuristics - the salience of particular problems to individuals who don't see the whole system. These ideas are also discussed in the work of Tversky and Kahneman (363).

Implementing a new policy requires a baseline assessment to identify the gap between recommended and current practice to identify the barriers to change and the practical actions required to implement the change. Ideally, corrective actions should make the 'right thing to do the easy thing to do' – something that using an infrastructure, such as a CTU organisation where there is a different hierarchical and team structure, may offer an option of a solution.

8.4.1 Quality appraisal of the case study

As part of the literature review, each of the studies that were included underwent quality appraisal (see Ch 2) using the CASP checklist (364)

I have used the same tool to appraise this study:

CASP appraisal tool (10 questions) (2)

- Was there a clear statement of the aims of the research?
- Is a qualitative methodology appropriate?
- Was the research design appropriate to address the aims of the research?
- Was the recruitment strategy appropriate to the aims of the research?
- Was the data collected in a way that addressed the research issue?
- Has the relationship between researcher and participants been adequately considered?
- Have ethical issues been taken into consideration?
- Was the data analysis sufficiently rigorous?
- Is there a clear statement of findings?
- How valuable is the research?

I assess the quality of this study on each point within the quality appraisal checklist below. A clear statement of the findings is provided as part of this thesis, and the value of the research discussed as part of the conclusions chapter. The case study appraisal is summarized as an appendix (Appendix 5).

According to the CASP appraisal tool – the quality of this study, and the reporting was that of “High” quality.

8.5 Autobiographical Reflection

The epistemological foundation of this research is based on the assumptions that the data collected and subsequent analysis are subject to various possible interpretations

and these are dependent on me as the researcher. It is impossible for me to separate myself from this research, as all of the data has been gathered, collated and interpreted by me, and has therefore been subject to the inherent bias of my position, background and knowledge.

Through my background of working as a clinician and junior doctor, and then as a role of research fellow as part of the case study trial, I did have a degree of familiarity of the clinical trial, and had worked with the core clinical trials team extensively prior to the commencement of this research study. My research ‘journey’ is described in more detail in Chapter 1. Through my role in the case study trial, my involvement in recruitment and shared disappointment in the trial’s failure – I did bring ‘pre-understandings’ to the research process.

The case study trial was my primary experience of the clinical trial management environment. Through working with individuals who were peers, and other members of the team that were significantly more experienced than me, this meant that the epistemological position taken in this research is one where the research process is inextricably bound up with the researcher, and that the construction of knowledge occurred jointly with the participants, a concept discussed in Freshwater and Avis 2004 (365).

As a result of my background, and the prior understanding that I had of the trial and its clinical context –I brought certain pre-conceptions and thoughts to the research process, as my thoughts and ideas were not something that I considered I could abstract from, (termed ‘bracketing’ according to Husserlian phenomenology) (366).

Freshwater and Avis (365) also dispute the concept of findings just ‘emerging’ from qualitative research. Gadamer (367) considered, that pre-understandings as prejudices should not be eliminated, but rather acknowledged in the process. In other words, pre-understandings are not necessarily misperceptions or distortions of the truth, but should be understood and accepted as conditions by which we encounter the world as we experience something. We bring these pre-understandings into the research process and they influence how we understand phenomena (368). Therefore, pre-understandings or biases are something we cannot completely ‘avoid’ or ‘bracket’ – a concept reinforced by the work of Finlay in 2003 –

“We should no longer work towards abolishing the presence of the researcher, instead subjectivity in research is transformed from a problem to an opportunity” (369)

I have attempted to take into account of my professional background and previous knowledge of the workings of the clinical trial, alongside that of the participants. As part of that process, I have attempted to reflect on my role in the interviews, and the influence that my own knowledge had on the collected data. It is inevitable that the interview participants had an influence on me, particularly in my position as a junior doctor and a junior member of the trial staff, with a very short history of involvement in the context of the management of a randomised clinical trial. With my limited experience of work in the area, and role as a trainee and junior member of staff, my approach was that of a novice – and in the hierarchical structure of a clinical trial, within a university and in a healthcare organisation – this is likely to have had an influence on the nature of the data gathered, and an effect on my approach to analysis.

Through having a critical approach and appreciation of my position in the context of pursuing this qualitative research study, I kept a reflective journal upon advice from my supervisors, which helped me to keep a continuous reflection on the process – both as a record of my experiences and feelings throughout the process, and how there may have been influences on the encounters in interviews. My position within this clinical trial as a clinical research fellow, and then later on as a participant researcher means that I had a unique position from which I could observe behaviours, develop rapport with individuals that were involved with the trial, and to interpret my findings. I believe that this unique insight has lent richness to the interpretation of the data that someone who was not already part of the trial team would not have been able to achieve.

9. Conclusions and recommendations

9.1 Conclusions

The overarching aim of this doctoral project was to explore the reasons behind clinical trial failure – through the examination of literature in the area, and through the analysis of this unique case study trial – and to learn lessons that could help to reduce the risk of trial failure in future practice.

The clinical trial was closed down due to its failure to attain recruitment targets. The literature review identified a series of study features that increased the likelihood of successful participant recruitment for clinical trials. Examination of the literature also identified the methods that had been used in the assessment of clinical trials in order to evaluate reasons for failure or delays in participant recruitment.

These recruitment targets were put in place through a meeting between the funding body and the chief investigator. Through this ‘post event’ evaluation, other issues have been examined, issues that have constituted violations of ‘Good Clinical Practice’, certain aspects of trial budget management, and those related to a lack of an established and experienced trial management infrastructure. These caused a varied impact and all had a role in causing delays, difficulty and increased costs for a project that failed to progress, and was therefore closed down.

This case study showed how fallible decisions at senior management level, allowed line management deficiencies within a project team and psychological precursors of unsafe acts. As a result, the project team made mistakes, lapses and GCP violations that might otherwise have been prevented. NHS trusts and HEIs have blind spots in project monitoring in a variety of ways, some of which are covered by the core competencies of trials units and contract research organisations. The involvement of a clinical trials unit or similar organisation does not guarantee success of a clinical trial, however, the involvement of a ‘research ready’ organisation with a stock of expertise and routines may reduce the risks of trial failure.

My case study has involved an innovative approach to analysis using a deductive framework based on social science theory. Social science theory is a useful way of considering the failure of RCTs (124). It has been used here, Reason (38) provides a useful framework which overcomes availability heuristics showing how the whole organisational system contributes to causal pathways associated with project failure, this model takes account of the ‘culture’ of an organisation, and characterises issues such as an ‘excessive authority gradient’ which can so often be an issue that increases the risk of error. My hope is that this innovative systems-based approach for post-hoc analysis of a failure of a clinical trial using a framework based on social science theory adds to the literature as it is an original concept, and the recommendations are based on addressing areas on an organizational level.

In this chapter I will discuss recommendations that have arisen from the research, and the potential real-world application for the prevention of adverse events in the

management of clinical trials. I will describe potential future research ideas and finish the chapter with some final reflections on the thesis.

9.2 Recommendations

In this section I describe how the findings of this case study may inform the design and conduct of future clinical trials in order to reduce the risk of trial failure.

Table 20 – Summary of key recommendations

Source	Broad Recommendation	Specific Focus
Literature review	Eliminate known factors associated with poor participant recruitment	• Factors relating to Study Design • Clinician and Participant factors • Factors relating to Research Environment
Case study	Adequate trial oversight	• Establishment of roles within the trials team and adherence to governance • Role of the organization • Role of the funder
Case study	Identification and mitigation of risks	• Maintenance of adequate risk register • Focus on culture of organization • Team working and supervision • Regular reporting and feedback

9.2.1 Focus on factors associated with poor participant recruitment

Key areas relating to the recruitment of trial participants identified as part of the literature review included ensuring a robust study design, availability of eligible participants and ensuring no additional issues relating to recruiting staff, and a research-ready environment.

It is a challenge to address all of these factors, however, many issues such as ‘the acceptability of the research intervention’, ‘availability of suitable research participants’ and ‘the suitability of the research environment’ could potentially be addressed through feasibility work or pilot studies prior to the formal commencement of the clinical trial.

Pilot studies are challenging in themselves – they usually require separate funding, and are usually only funded for a few months. Because of their short-term nature, in an institution that is small, or does not have the pool of available research-ready staff such as in a CTU environment or similar – the provision and recruitment of short term staff in order to run a pilot trial can be challenging for an organization.

Formal pilot and feasibility work is a requirement now with many of the dominant research funding bodies. It allows for resource planning and risk assessment. The case study trial did not have any formal pilot or feasibility work built in – which was a significant finding and did expose the trial to a risk of failure.

9.2.2 Adequate trial oversight

One of the significant deficiencies identified in the case study trial was the lack of trial oversight. One of the ways of mitigating this risk would be through focus on the trials management team, and the establishment of roles and responsibilities. Clinical trials governance ensures accountability, the smooth running of a project and adherence to sound ethical practices (187). Although there was evidence of some documentation relating to trials governance – there was insufficient oversight of the

project, poor establishment of adherence to processes, and no clear lines of responsibility or accountability.

The recommendation for future best practice for trials management would be that of establishing a robust governance structure, with clear responsibilities including the establishment of the role of the team, that of the organization and the role of the funder to ensure best practice is followed. The role of feedback loops in preventing error has been explained at length in the discussion chapter, and consideration of the establishment of regular progress reports into regular trials management practice in order to maintain a culture of openness may also reduce project risk. Regular reviews of progress would help project management teams to control the project, and allow stakeholders and managers to compare what is actually happening on the project with what they would like to happen (370). Controlling the project or clinical trial in this way allows timely decisions at the right level of the organization to take place, either about whether a piece of work should proceed, or how to handle problems in the project.

9.2.3 Identification and mitigation of risk

A key part of preventing adverse events is to be alert to the potential risks that may occur, and prompt preventative action. The case study trial did not have systems in place to detect potential error or to address it, but one recommendation would be for future trials to consider the introduction and maintenance of a ‘Risk Register’

In the field of patient safety, The Institute of Medicine’s *To Err Is Human* (371) and the Department of Health’s *Organisation with a memory* (372) reports suggest that

one prerequisite for learning from and preventing failures is a clear system of understanding of the range and number of failures that are occurring in a system. Therefore, one of the key recommendations of both reports was the introduction of a reporting scheme for adverse events and near misses in healthcare, to provide a database of errors and allow for the identification of areas of particular concern. In England one of the primary functions of the National Patient Safety Agency (NPSA), now NHS Improvement, was the development of a reporting system (National Reporting and Learning System) (373).

In the field of project management, risk management is seen as a key part of governance. In many industries risk profile is attributed to a cost – a financial value that can be linked to each part of the process within a project. Identification of potential risks to a project are collected through a number of processes, including brainstorming meetings, expert opinions, and from other sources such as reporting systems (374). This activity is performed at the planning stage of a project, and as the project is dynamic and risks may change with time and progress, regular reviews are also performed throughout the project timeline alongside considerations of how to address and mitigate risk at each point (375).

Regular consideration of risk, putting risk management processes in place in order to identify suitable responses to risk, and monitoring and reporting of risk factors in a risk register or risk log is essential practice to ensure safety and to maintain standards of governance, regardless of the size of the project being undertaken. It should be promoted as best practice in the management of clinical trials.

9.3 Unanswered Questions and Future Research

This thesis and the literature review has primarily focused on trials that have gone badly – an exploration of those clinical trials that have been particularly successful would be an interesting addition to the information gleaned from the literature as part of this thesis. Specifically, whether there were any particular features of successful trials that made them more likely to do well. This question has been asked in the past, by the STEPS investigators (376), where there was an attempt to characterize those factors that were present in trials that recruited successfully and contrast with those trials that failed to recruit. This investigation did not yield sufficiently definitive results to make strong recommendations, but did suggest that future trials consider the different needs of a trial in different phases – the complexity of large trials means that unanticipated difficulties are highly likely at some time in every trial.

Future research should focus on refining the approach used in this case study analysis, and applying it to future clinical trials. It could be applied to different types of research studies, and examine those that have failed for reasons other than a failure to recruit. There are many types of research study that may benefit from using this as a risk management or assessment tool in order to develop studies - it could also be applied by host institutions in order to assess and manage the risk associated with proposed and funded projects.

The aim of future research should work towards addressing the question of how funders and host institutions assess investigators as fit and proper persons for leading research projects - which often involve the investment of seven figure sums of public

money. The case study trial was unique in that it demonstrated failure at all levels. Not all errors were high up in the organisations involved, and although there were various levels where there could be fail-safes, there were none. The novel utilization of the model of Organizational Accidents (40) in this scenario, together with future qualitative research into current best practice in the public and private sector institutions that demonstrate successful research outcomes may assist in the development of a robust risk assessment tool that can be applied to new research projects.

9.4 Final Reflections

Clinical trials management is challenging. Many clinical trials do fail to progress, and this can lead to significant ethical and financial issues. There is evidence in the literature, and research that has been done in the past where there has been a focus on the challenges that clinical trials face, particularly when it comes to participant recruitment. All clinical trials are complex, and all face considerable risk.

The case study trial demonstrated several areas where potential errors could take place, but as a result of poor oversight and ownership, potential errors went unchecked leading to a chain of events that led to catastrophic failure.

Prevention of failure in future trials would depend on:

- Adequate planning, including consideration of risk management and focus on mitigation of potential risk.

- Maintenance of an open organizational culture with eradication of an excessive authority gradient where reporting of risk and concerns is encouraged.
- Well-maintained governance processes with clear roles to ensure quality and safety
- Team-based supportive empowerment and responsibility in order to ensure that there is never one individual responsible for all decision making.

It is important that there is recognition of the issues identified as part of this research, and that they provide areas where change can be focused for the benefit of clinical trials management teams, clinicians and all participants in clinical research.

1. : The Center for Evidence-Based Management (CEBMA); 2017 [Available from: <https://www.cebma.org/>].
2. Programme CAS. 10 questions to help you make sense of qualitative research. Milton Keynes Primary Care Trust Milton Keynes; 2002.
3. Bull JP. The Historical Development of Clinical Therapeutic Trials. *Journal of Chronic Diseases*. 1959;10(3):218-48.
4. Concato J, Nirav Shah, and Ralph I. Horwitz. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *The New England journal of medicine*. 2000;342(25):1887-92.
5. Jadad A. *Randomised Controlled Trials - A Users Guide*: BMJ Publishing Group; 1998.
6. Schulz KF, Grimes DA. Generation of allocation sequences in randomised trials: chance, not choice. *The Lancet*. 2002;359(9305):515-9.
7. Krzyzanowska MK, Kaplan R, Sullivan R. How may clinical research improve healthcare outcomes? *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2011;22 Suppl 7:vii10-vii5.
8. Clark AL, Lammiman MJ, Goode K, Cleland JG. Is taking part in clinical trials good for your health? A cohort study. *European journal of heart failure*. 2009;11(11):1078-83.
9. Sciences TAoM. *Medical Research : Assessing the benefits to society*. In: Trust W, editor. 2006.
10. Buxton M, Steve Hanney, and Teri Jones. . Estimating the economic value to societies of the impact of health research: a critical review. *Bulletin of the World Health Organization*. 2004;82.10:733-9.
11. Robinson M, Cook S. *Clinical Trials Risk Management*: CRC Press; 2005.
12. Sibbald B, and Martin Roland. Understanding controlled trials. Why are randomised controlled trials important? *British Medical Journal*. 1998;316(7126):201.
13. Williams; RJ, Tse; T, DiPiazza; K, Zarin. DA. Terminated trials in the ClinicalTrials. gov results database: evaluation of availability of primary outcome data and reasons for termination. *PloS one*. 2015;10(5).
14. Khalid Abozguia, Thanh Trung Phan, Shivu GN. Insights into how to conduct a clinical trial in the UK. *J R Soc Med*. 2007;100(10):469-72.
15. Cooksey SD. A review of UK health research funding. In: Treasury H, editor. *The Stationary Office: Her Majesty's Stationary Office*; 2006.
16. Association. WM. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. *Journal of the American Medical Association*. 2013;310(20):2191-4.
17. RJ Prescott CC, WJ Gillespie, AM Grant, IT Russell, S Kiauka, IR Colthart, S Ross, SM Shepherd, D Russell. Factors that Limit the quality, number and progress of randomised controlled trials. *Health technology assessment*. 1999;3.
18. Walters SJ, Bonacho Dos Anjos Henriques-Cadby I, Bortolami O, Flight L, Hind D, Jacques RM, et al. Recruitment and retention of participants in randomised controlled trials: a review of trials funded and published by the United Kingdom Health Technology Assessment Programme. *BMJ open*. 2017;7(3):e015276.
19. McDonald AM, Treweek S, Shakur H, Free C, Knight R, Speed C, et al. Using a business model approach and marketing techniques for recruitment to clinical trials. *Trials [Electronic Resource]*. 2011;12:74.

20. Sully BG, Julious SA, Nicholl J. A reinvestigation of recruitment to randomised, controlled, multicenter trials: a review of trials funded by two UK funding agencies. *Trials* [Electronic Resource]. 2013;14:166.
21. McDonald AM, Knight RC, Campbell MK, Entwistle VA, Grant AM, Cook JA, et al. What influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies. *Trials*. 2006;7:9.
22. Sackett DL, and John Hoey. Why randomized controlled trials fail but needn't: a new series is launched. *Canadian Medical Association Journal*. 2000;162.9:1301-2.
23. Smyth RL. Lessons to be learnt from unsuccessful clinical trials. *Thorax*. 2011;66(6):459-60.
24. Easterbrook PJ, and D. R. Matthews. Fate of research studies. *Journal of Royal Society of Medicine*. 1992;85(2):71-6.
25. Fletcher B, Gheorghe A, Moore D, Wilson S, Damery S. Improving the recruitment activity of clinicians in randomised controlled trials: a systematic review. *BMJ open*. 2012;2(1):e000496.
26. Lembitz A, Clarke TJ. Clarifying "never events" and introducing "always events". *Patient Safety in Surgery*. 2009;3(1):26.
27. Law RL, Pullyblank AM, Eveleigh M, Slack N. Avoiding never events: improving nasogastric intubation practice and standards. *Clinical radiology*. 2013;68(3):239-44.
28. Wu AW, Lipshutz AM, Pronovost PJ. Effectiveness and efficiency of root cause analysis in medicine. *JAMA : the journal of the American Medical Association*. 2008;299(6):685-7.
29. Stahel PF, Sabel AL, Victoroff MS, et al. Wrong-site and wrong-patient procedures in the universal protocol era: Analysis of a prospective database of physician self-reported occurrences. *Archives of Surgery*. 2010;145(10):978-84.
30. Zidel T. *A Lean Guide to Transforming Healthcare: How to Implement Lean Principles in Hospitals, Medical Offices, Clinics, and Other Healthcare Organizations*: Taylor & Francis; 2006.
31. Ohno T. *Toyota production system: beyond large-scale production*: crc Press; 1988.
32. Card AJ. The problem with '5 whys'. *BMJ quality & safety*. 2016.
33. Plsek PE, Greenhalgh T. Complexity science: The challenge of complexity in health care. *BMJ: British Medical Journal*. 2001;323(7313):625.
34. Clancy TR, Delaney CW. Complex nursing systems. *Journal of nursing management*. 2005;13(3):192-201.
35. Helmreich RL. On error management: lessons from aviation. *British Medical Journal*. 2000;320:781.
36. Gale N HG, Cameron E, Rashid S, Redwood S. . Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Medical Research Methodology* 2013;13(1):117.
37. ICH. Guideline for Good Clinical Practice. ICH Harmonised Tripartite Guideline 1996;E6(R1).
38. Reason J. *Human error*: Cambridge university press; 1990.
39. Sasou K, Reason J. Team errors: definition and taxonomy. *Reliability Engineering & System Safety*. 1999;65(1):1-9.
40. Reason J. *Human error: Models and management*. . *British Medical Journal*. 2000;320(768-770).

41. Leape LL, Berwick DM. Five years after To Err Is Human: what have we learned? *JAMA : the journal of the American Medical Association*. 2005;293(19):2384-90.
42. Lucian L Leape DMB. Safe Health Care, Are We Up To It? *Bmj*. 2000;320:725-6.
43. Helmreich RL, Davies JM. Culture, threat, and error: lessons from aviation. *Canadian Journal of Anesthesia/Journal canadien d'anesthésie*. 2004;51:R1-R4.
44. Sexton JB, Thomas EJ, Helmreich RL. Error, stress, and teamwork in medicine and aviation: cross sectional surveys. *Bmj*. 2000;320(7237):745-9.
45. Chalmers I, Michael B. Bracken, Ben Djulbegovic, Silvio Garattini, Jonathan Grant, A. Metin Gülmezoglu, David W. Howells, John Ioannidis, and Sandy Oliver. How to increase value and reduce waste when research priorities are set. *The Lancet*. 2014;383(9912):156-65.
46. Psaty BM, Rennie D. Stopping medical research to save money: A broken pact with researchers and patients. *JAMA : the journal of the American Medical Association*. 2003;289(16):2128-31.
47. Carlisle B, Kimmelman J, Ramsay T, MacKinnon N. Unsuccessful trial accrual and human subjects protections: an empirical analysis of recently closed trials. *Clinical Trials*. 2015;12(1):77-83.
48. Ramsey S, Scoggins J. Commentary: practicing on the tip of an information iceberg? Evidence of underpublication of registered clinical trials in oncology. *The oncologist*. 2008;13(9):925-9.
49. Kasenda B, von Elm EB, You J, Blümle A, Tomonaga Y, Saccilotto R, et al. Learning from failure-rationale and design for a study about discontinuation of randomized trials (DISCO study). *BMC medical research methodology*. 2012;12(1):131.
50. Cheng SK, Dietrich MS, Dilts DM. A sense of urgency: Evaluating the link between clinical trial development time and the accrual performance of cancer therapy evaluation program (NCI-CTEP) sponsored studies. *Clin Cancer Res*. 2010;16(22):5557-63.
51. Bernardez-Pereira S, Lopes RD, Carrion MJ, Santucci EV, Soares RM, de Oliveira Abreu M, et al. Prevalence, characteristics, and predictors of early termination of cardiovascular clinical trials due to low recruitment: insights from the ClinicalTrials.gov registry. *American heart journal*. 2014;168(2):213-9 e1.
52. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine*. 2009;6(7):e1000097.
53. Hopewell S, Clarke M, Lefebvre C, Scherer R. Handsearching versus electronic searching to identify reports of randomized trials. *The Cochrane database of systematic reviews*. 2007(2):MR000001.
54. Sandelowski M DS, Emden C. Focus on qualitative methods. *Qualitative metasynthesis: issues and techniques*. . *Research in Nursing & Health*. 1997;20:365-71.
55. Ritchie J, Spencer L. Qualitative data analysis for applied policy research. In: Bryman A, Burgess RG, editors. *Analyzing Qualitative Data*. London: Routledge; 1994.
56. Hill A, Spittlehouse C. What is critical appraisal?: Citeseer; 2001.
57. Cohen DJ, Crabtree BF. Evaluative criteria for qualitative research in health care: controversies and recommendations. *The Annals of Family Medicine*. 2008;6(4):331-9.

58. Dixon-Woods M, Sutton A, Shaw R, Miller T, Smith J, Young B, et al. Appraising qualitative research for inclusion in systematic reviews: a quantitative and qualitative comparison of three methods. *Journal of health services research & policy*. 2007;12(1):42-7.
59. Keightley A, Clarkson J, Maguire A, Speed C, Innes N. Participant recruitment to FiCTION, a primary dental care trial - survey of facilitators and barriers. *British dental journal*. 2014;217(10):E22.
60. Howard L, de Salis I, Tomlin Z, Thornicroft G, Donovan J. Why is recruitment to trials difficult? An investigation into recruitment difficulties in an RCT of supported employment in patients with severe mental illness. *Contemp Clin Trials*. 2009;30(1):40-6.
61. Shilling V, Williamson, P. R., Hickey, H., Sowden, E., Smyth, R. L., & Young, B. Processes in recruitment to randomised controlled trials of medicines for children (RECRUIT): a qualitative study. . *Health technology assessment*. 2011;15(24):1-116.
62. Donovan JL, S. Parmasivan, Isabel de Salis, and M. Torrien. . Clear obstacles and hidden challenges: understanding recruiter perspectives in six pragmatic randomised controlled trials. *Trials*. 2014;15(1):5.
63. Donovan JL, de Salis I, Toerien M, Paramasivan S, Hamdy FC, Blazeby JM. The intellectual challenges and emotional consequences of equipoise contributed to the fragility of recruitment in six randomized controlled trials. *J Clin Epidemiol*. 2014;67(8):912-20.
64. Strong S, Paramasivan S, Mills N, Wilson C, Donovan JL, Blazeby JM. 'The trial is owned by the team, not by an individual': a qualitative study exploring the role of teamwork in recruitment to randomised controlled trials in surgical oncology. *Trials*. 2016;17(1):212.
65. Hamilton DW, de Salis I, Donovan JL, Birchall M. The recruitment of patients to trials in head and neck cancer: a qualitative study of the EaStER trial of treatments for early laryngeal cancer. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery*. 2013;270(8):2333-7.
66. Potter R, Dale, J., & Caramlau, I. . A qualitative study exploring practice nurses' experience of participating in a primary care-based randomised controlled trial. *Journal of Research in Nursing*. 2009;14(5):439-47.
67. Ziebland S, Featherstone K, Snowdon C, Barker K, Frost H, Fairbank J. Does it matter if clinicians recruiting for a trial don't understand what the trial is really about? Qualitative study of surgeons' experiences of participation in a pragmatic multi-centre RCT. *Trials*. 2007;8:4.
68. Fairhurst K, & Dowrick, C. . Problems with recruitment in a randomized controlled trial of counselling in general practice: causes and implications. . *Journal of Health Services Research*. 1996;1(2):77-80.
69. Stuart J, Barnes J, Spiby H, Elbourne D. Understanding barriers to involving community midwives in identifying research participants; experience of the first steps randomised controlled trial. *Midwifery*. 2015;31(8):779-86.
70. Maslin-Prothero S. The role of the multidisciplinary team in recruiting to cancer clinical trials. *European journal of cancer care*. 2006;15(2):146-54.
71. Goodwin PJ, Leszcz, M., Quirt, G., Koopmans, J., Arnold, A., Dohan, E., ... & Navarro, M. Lessons learned from enrollment in the BEST study—A multicenter,

- randomized trial of group psychosocial support in metastatic breast cancer. . *Journal of clinical epidemiology*. 2000;53(1):47-55.
72. Pike NA, Pemberton V, Allen K, Jacobs JP, Hsu DT, Lewis AB, et al. Challenges and successes of recruitment in the "angiotensin-converting enzyme inhibition in infants with single ventricle trial" of the Pediatric Heart Network. *Cardiol Young*. 2013;23(2):248-57.
 73. Lannin N, & Cusick, A. . Factors affecting patient recruitment in an acute rehabilitation randomized controlled trial. . *American Journal of Occupational Therapy*. 2006;60(2):177-81.
 74. Trussell JC, Christman GM, Ohl DA, Legro RS, Krawetz SA, Snyder PJ, et al. Recruitment challenges of a multicenter randomized controlled varicocelelectomy trial. *Fertil Steril*. 2011;96(6):1299-305.
 75. Blanton S, Morris DM, Prettyman MG, McCulloch K, Redmond S, Light KE, et al. Lessons learned in participant recruitment and retention: the EXCITE trial. *Phys Ther*. 2006;86(11):1520-33.
 76. De Wit NJ, A. Otto Quartero, A. P. Zuithoff, and Mattijs E. Numans. . Participation and successful patient recruitment in primary care. *The Journal of family practice*. 2001;50(11):976-.
 77. Spaar A, Frey M, Turk A, Karrer W, Puhan MA. Recruitment barriers in a randomized controlled trial from the physicians' perspective: a postal survey. *BMC Med Res Methodol*. 2009;9:14.
 78. Page MJ, French, S. D., McKenzie, J. E., O'Connor, D. A., & Green, S. E. Recruitment difficulties in a primary care cluster randomised trial: investigating factors contributing to general practitioners' recruitment of patients. . *BMC medical research methodology*. 2011;11(1):35.
 79. Laegreid IK, Aasarod K, Jordhoy M. End-stage renal disease and recruitment to randomized trials: why is it so difficult? Results from a survey among Norwegian nephrologists. *Scand J Urol Nephrol*. 2011;45(4):285-9.
 80. Geynisman DM, Szmulewitz RZ, Stadler WM. A trial postmortem: challenges in conducting a randomized, double-blind, phase 2 study in men with castration-resistant prostate cancer. *Eur Urol*. 2012;62(5):864-6.
 81. Costescu DJ, & Cullimore, A. J. Lessons learned from a resident-led clinical trial in obstetrics. *Clinical trials*. 2013;10(4):612-6.
 82. Ferris M, Norwood V, Radeva M, Gassman JJ, Al-Uzri A, Askenazi D, et al. Patient recruitment into a multicenter randomized clinical trial for kidney disease: report of the focal segmental glomerulosclerosis clinical trial (FSGS CT). *Clin Transl Sci*. 2013;6(1):13-20.
 83. Foster JM, Sawyer SM, Smith L, Reddel HK, Usherwood T. Barriers and facilitators to patient recruitment to a cluster randomized controlled trial in primary care: lessons for future trials. *BMC Med Res Methodol*. 2015;15:18.
 84. Bower P, Wilson S, Mathers N. Short report: how often do UK primary care trials face recruitment delays? *Family practice*. 2007;24(6):601-3.
 85. Rendell JM, Merritt RD, Geddes JR. Incentives and disincentives to participation by clinicians in randomised controlled trials. *The Cochrane database of systematic reviews*. 2007(2):MR000021.
 86. Charlson ME, and Ralph I. Horwitz. . Applying results of randomised trials to clinical practice: impact of losses before randomisation. *Bmj*. 1984;289(6454):1281-84.
 87. Lasagna L. Problems in publcatlon of clinical trial methodology. *Clinical Pharmacology & Therapeutics*. 1979;25(5part2):751-3.

88. Gorringer JAL. Initial preparation for clinical trials. E.L. Harris JDF, editor. Edinburgh/London: Livingstone; 1970.
89. van der Wouden JC, Blankenstein AH, Huibers MJH, van der Windt DAWM, Stalman WAB, Verhagen AP. Survey among 78 studies showed that Lasagna's law holds in Dutch primary care research. *Journal of Clinical Epidemiology*. 60(8):819-24.
90. White D, Hind D. Projection of participant recruitment to primary care research: a qualitative study. *Trials*. 2015;16:473.
91. Hunninghake DB, Charles A. Darby, and Jeffrey L. Probstfield. Recruitment experience in clinical trials: literature summary and annotated bibliography. *Control Clin Trials*. 1987;8(4):6-30.
92. Lovato LC, Hill K, Hertert S, Hunninghake DB, JL. P. Recruitment for controlled clinical trials: literature summary and annotated bibliography. *Controlled Clinical Trials*. 1997;4(18):328-52.
93. Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to participation in Randomised Controlled Trials : A systematic review. *Journal of Clinical Epidemiology*. 1999;52(12):1143-1156.
94. Toohar RL, Middleton PF, Crowther CA. A thematic analysis of factors influencing recruitment to maternal and perinatal trials. *BMC Pregnancy Childbirth*. 2008;8:36.
95. Hill AB. Medical ethics and controlled trials. *British medical journal*. 1963;5337(1):1043.
96. Borschmann R, Patterson S, Poovendran D, Wilson D, Weaver T. Influences on recruitment to randomised controlled trials in mental health settings in England: a national cross-sectional survey of researchers working for the Mental Health Research Network. *BMC Medical Research Methodology*. 2014;14:23.
97. Lenney W, Perry S, Price D. Clinical trials and tribulations: the MASCOT study. *Thorax*. 2011;66(6):457-8.
98. Kearney A, McKay A, Hickey H, Balabanova S, Marson AG, Gamble C, et al. Opening research sites in multicentre clinical trials within the UK: a detailed analysis of delays. *BMJ open*. 2014;4(9):e005874.
99. Mallick AA, O'Callaghan FJK. Research governance delays for a multi-centre non-interventional study. *J R Soc Med*. 2009;102.
100. Croghan IT, Viker SD, Limper AH, Evans TK, Cornell AR, Ebbert JO, et al. Developing a clinical trial unit to advance research in an academic institution. *Contemp Clin Trials*. 2015;45(Pt B):270-6.
101. Gohel MS, Chetter I. Are clinical trials units essential for a successful trial? *Bmj*. 2015;350:h2823.
102. McFadden E, Bashir S, Canham S, Darbyshire J, Davidson P, Day S, et al. The impact of registration of clinical trials units: the UK experience. *Clinical trials (London, England)*. 2015;12(2):166-73.
103. Treweek S, Lockhart P, Pitkethly M, Cook JA, Kjeldstrom M, Johansen M, et al. Methods to improve recruitment to randomised controlled trials: Cochrane systematic review and meta-analysis. *BMJ open*. 2013;3(2).
104. Treweek S, Mitchell E, Pitkethly M, Cook J, Kjeldstrøm M, Johansen M, et al. Strategies to improve recruitment to randomised controlled trials. *Cochrane Database of Systematic Reviews [Internet]*. 2010; (4). Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.MR000013.pub5/abstract>.
105. Watson JM, Torgerson DJ. Increasing recruitment to randomised trials: a review of randomised controlled trials. *BMC Med Res Methodol*. 2006;6:34.

106. Farrell B, Kenyon S, Shakur H. Managing clinical trials. *Trials*. 2010;11:78.
107. Francis D, Roberts I, Elbourne DR, Shakur H, Knight RC, Garcia J, et al. Marketing and clinical trials: a case study. *Trials*. 2007;8:37.
108. Palmer R, Harrison M, Cross E, Enderby P. Negotiating excess treatment costs in a clinical research trial: the good, the bad and the innovative. *Trials*. 2016;17:71.
109. Gheorghe A, Roberts TE, Ives JC, Fletcher BR, Calvert M. Centre selection for clinical trials and the generalisability of results: a mixed methods study. *PloS one*. 2013;8(2):e56560.
110. Gheorgiade M, Vaduganathan M, Greene SJ, Mentz RJ, Adams KF, Anker SD, et al. Site selection in global clinical trials in patients hospitalized for heart failure: perceived problems and potential solutions. *Heart Fail Rev*. 2014;19(2):135-52.
111. Snooks H, Hutchings H, Seagrove A, Stewart-Brown S, Williams J, Russell I. Bureaucracy stifles medical research in Britain: a tale of three trials. *BMC Medical Research Methodology*. 2012;12(1):122.
112. [REDACTED]
113. [REDACTED]
114. [REDACTED]
115. [REDACTED]
116. [REDACTED]
117. [REDACTED]
118. [REDACTED]
119. [REDACTED]
120. [REDACTED]
121. [REDACTED]

122. [REDACTED]
123. NIHR. The Clinical trials toolkit - Routemap 2013 [updated August 2013]. 1.1:[Available from: <http://www.ct-toolkit.ac.uk/routemap>.
124. Vaughan D. The dark side of organizations: Mistake, misconduct, and disaster. *Annual review of sociology*. 1999;25(1):271-305.
125. Vaughan D. The Challenger launch decision: Risky culture, technology, and deviance at NASA. Chicago: The University of Chicago Press; 1996.
126. Hohenemser C. The accident at Chernobyl: health and environmental consequences and the implications for risk management. *Annual Review of Energy*. 1988;13(1):383-428.
127. Leape LL, Brennan TA, Laird N, Lawthers AG, Localio AR, Barnes BA, et al. The nature of adverse events in hospitalized patients: results of the Harvard Medical Practice Study II. *New England journal of medicine*. 1991;324(6):377-84.
128. West E. Organisational sources of safety and danger: sociological contributions to the study of adverse events. *BMJ quality & safety*. 2000;9(2):120-6.
129. Vincent C. Clinical risk management: Enhancing patient safety: BMJ Publishing group; 2001.
130. Vincent C. Risk, safety, and the dark side of quality. *BMJ: British Medical Journal*. 1997;314(7097):1775.
131. West E. Sociological contributions to patient safety. *Patient safety: Research into practice*. 2006:19-30.
132. Leape LL. A systems analysis approach to medical error. *Journal of evaluation in clinical practice*. 1997;3(3):213-22.
133. Hughes EC. Mistakes at work. *Canadian Journal of Economics and Political Science/Revue canadienne de economiques et science politique*. 1951;17(3):320-7.
134. Perrow C. A personal note on normal accidents. *Organization & environment*. 2004;17(1):9-14.
135. Lawton R, Parker D. Individual differences in accident liability: A review and integrative approach. *Human Factors*. 1998;40(4):655-71.
136. Reason J, Parker D, Lawton R. Organizational controls and safety: The varieties of rule - related behaviour. *Journal of occupational and organizational psychology*. 1998;71(4):289-304.
137. Parker D, Lawton R. Psychological approaches to patient safety. *Patient safety: Research into practice*. 2006:31-40.
138. Reason J. Understanding adverse events: human factors. *Quality in Health Care* 1995;4:80-9.
139. Vincent NS, Sally Taylor-Adams, Charles. Developing a systematic method of analysing serious incidents in mental health. *Journal of mental health*. 2000;9(1):89-103.
140. Weick KE. Organizational culture as a source of high reliability. *California management review*. 1987;29(2):112-27.
141. Weick KE, Sutcliffe KM, Obstfeld D. Organizing for high reliability: Processes of collective mindfulness. *Crisis management*. 2008;3(1):81-123.
142. Webb R, Currie M, Morgan C, Williamson J, Mackay P, Russell W, et al. The Australian Incident Monitoring Study: an analysis of 2000 incident reports. *Anaesthesia and intensive care*. 1993;21:520-.
143. Norman DA. Design rules based on analyses of human error. *Communications of the ACM*. 1983;26(4):254-8.

144. Rasmussen J, P. Nixon, and F. Warner. Human error and the problem of causality in analysis of accidents [and discussion]. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*. 1990;327(1241):449-62.
145. Kluger M, Tham E, Coleman N, Runciman W, Bullock M. Inadequate pre-operative evaluation and preparation: a review of 197 reports from the Australian Incident Monitoring Study. *Anaesthesia*. 2000;55(12):1173-8.
146. Beckmann U, Baldwin I, Hart G, Runciman W. The Australian Incident Monitoring Study in Intensive Care: AIMS-ICU. An analysis of the first year of reporting. 1996.
147. Morgan H, Priest P. Suicide and other unexpected deaths among psychiatric in-patients: The Bristol confidential inquiry. *The British Journal of Psychiatry*. 1991;158(3):368-74.
148. Hunt IM, Kapur N, Webb R, Robinson J, Burns J, Turnbull P, et al. Suicide in current psychiatric in-patients: a case-control study The National Confidential Inquiry into Suicide and Homicide. *Psychological medicine*. 2007;37(6):831-7.
149. Fleming PJ, Blair PS, Bacon C, Bensley D, Smith I, Taylor E, et al. Environment of infants during sleep and risk of the sudden infant death syndrome: results of 1993-5 case-control study for confidential inquiry into stillbirths and deaths in infancy. *Bmj*. 1996;313(7051):191-5.
150. Payne J, Milner P, Saul C, Bowns I, Hannay D, Ramsay L. Local confidential inquiry into avoidable factors in deaths from stroke and hypertensive disease. *Bmj*. 1993;307(6911):1027-30.
151. Woloshynowych M, Rogers S, Taylor-Adams S, Vincent C. The investigation and analysis of critical incidents and adverse events in healthcare. 2005.
152. Flanagan JC. The critical incident technique. *Psychological bulletin*. 1954;51(4):327.
153. Cooper JB, Newbower RS, Long CD, McPeck B. Preventable anesthesia mishaps: a study of human factors. *Anesthesiology*. 1978;49(6):399-406.
154. Cooper JB, Newbower RS, Long CD, McPeck B. Preventable anesthesia mishaps: a study of human factors. *BMJ quality & safety*. 2002;11(3):277-82.
155. Cooper JB, Newbower RS, Kitz RJ. An analysis of major errors and equipment failures in anesthesia management: considerations for prevention and detection. *Anesthesiology*. 1984;60(1):34-42.
156. Short T, O'regan A, Lew J, Oh T. Critical incident reporting in an anaesthetic department quality assurance programme. *Anaesthesia*. 1993;48(1):3-7.
157. Pringle M. Significant event auditing. *Scandinavian journal of primary health care*. 2000;18(4):200-2.
158. Pringle M, Bradley C, Carmichael C, Wallis H, Moore A. Significant event auditing. A study of the feasibility and potential of case-based auditing in primary medical care. Occasional paper (Royal College of General Practitioners). 1995(70):i.
159. Robinson L, Stacy R, Spencer J, Bhopal R. Use facilitated case discussions for significant event auditing. *BMJ: British Medical Journal*. 1995;311(7000):315.
160. Westcott R, Sweeney G, Stead J. Significant event audit in practice: a preliminary study. *Family practice*. 2000;17(2):173-9.
161. Gillam S, Siriwardena AN. Frameworks for improvement: clinical audit, the plan-do-study-act cycle and significant event audit. *Quality in Primary Care*. 2013;21(2).

162. Wilson T, Pringle M, Sheikh A. Promoting patient safety in primary care: research, action, and leadership are required. British Medical Journal Publishing Group; 2001.
163. Wu AW, Lipshutz AK, Pronovost PJ. Effectiveness and efficiency of root cause analysis in medicine. *Journal of the American Medical Association*. 2008;299:685-7.
164. C.J. Eagle, J.M. Davies, Reason JT. Accident analysis of large scale technological disasters: applied to anaesthetic complications. *Canadian Journal of Anaesthesia*. 1992;39:118-22.
165. Shojania KG, Duncan BW, McDonald KM, Wachter RM, Markowitz A. Making health care safer: a critical analysis of patient safety practices. *Evid Rep Technol Assess (Summ)*. 2001;43(1):668.
166. Dineen M. Six steps to root cause analysis: Consequence; 2011.
167. : NHS Improvement; 2015 [Available from: <https://improvement.nhs.uk/resources/serious-incident-framework/>].
168. Jimmerson C, Weber D, Sobek II DK. Reducing waste and errors: piloting lean principles at Intermountain Healthcare. *The Joint Commission Journal on Quality and Patient Safety*. 2005;31(5):249-57.
169. Vincent C. Analysis of clinical incidents: a window on the system not a search for root causes. BMJ Publishing Group Ltd; 2004.
170. Reason J. Managing the risks of organizational accidents: Routledge; 2016.
171. Reason J. Safety paradoxes and safety culture. *Injury Control and Safety Promotion*. 2000;7(1):3-14.
172. Stanhope N, Vincent CA, Taylor-Adams SE, O'Connor AM, Beard RW. Applying human factors methods to clinical risk management in obstetrics. *British Journal of Obstetrics and Gynaecology*. 1997;104:1225-32.
173. Vincent C, Taylor-Adams S, Stanhope N. Framework for analysing risk and safety in clinical medicine. *BMJ: British Medical Journal*. 1998;316(7138):1154.
174. Taylor-Adams S, Vincent C, Stanhope N. Applying human factors methods to the investigation and analysis of clinical adverse events. *Safety Science*. 1999;31(2):143-59.
175. Zhi H. Risk management for overseas construction projects. *International journal of project management*. 1995;13(4):231-7.
176. Health Do. Research governance framework for health and social care. 2009.
177. Council MR. MRC Guidelines for Good Clinical Practice in Clinical Trials. . London: MRC, 1998.
178. Leon AC, Davis LL, Kraemer HC. The Role and Interpretation of Pilot Studies in Clinical Research. *Journal of psychiatric research*. 2011;45(5):626-9.
179. Daykin A, Selman LE, Cramer H, McCann S, Shorter GW, Sydes MR, et al. What are the roles and valued attributes of a Trial Steering Committee? Ethnographic study of eight clinical trials facing challenges. *Trials*. 2016;17(1):307.
180. Harman NL. Exploring the role and function of trial steering committees: results of an expert panel meeting. . *Trials*. 2015;16(1):597.
181. Reason J, Hollnagel E, Paries J. Revisiting the "Swiss Cheese" Model of accidents. 2006.
182. Reason J, Andersen H, editors. Errors in a team context. Mohawc Belgirate Workshop; 1991.
183. Reason J. Latent errors and systems disasters. *Human error*. Cambridge, UK: Cambridge University Press; 1990. p. 173-216.

184. Reason J. The Contribution of Latent Human Failures to the Breakdown of Complex Systems. *Philosophical Transactions of the Royal Society of London*. 1990;327(1241):475-84.
185. Reason J. Achieving a safe culture: theory and practice. *Work & Stress*. 1998;12(3):293-306.
186. Reason J. Types, tokens and indicators. *Proceedings of the Human Factors Society Annual Meeting*. 1990;34(12):885-9.
187. Gray C. What is clinical governance? *Bmj*. 2005;330(7506):s254-s.
188. Ziller RC. Four techniques of group decision making under uncertainty. *Journal of Applied Psychology*. 1957;41(6):384-8.
189. Patrick A. Palmieri PRDLTPTEOAG. The anatomy and physiology of error in adverse health care events: Emerald Group Publishing Limited; 2008. 33-68 p.
190. Ummerhofer W, Amsler F, Sutter PM, Martina B, Martin J, Scheidegger D. Team performance in the emergency room: assessment of inter-disciplinary attitudes. *Resuscitation*. 2001;49(1):39-46.
191. Ziller RC. Scales of Judgment: A Determinant of the Accuracy of Group Decisions. *Human Relations*. 1955;8(2):153-64.
192. Ritchie J, Lewis J, Nicholls CM, Ormston R. *Qualitative research practice: A guide for social science students and researchers*: Sage; 2013.
193. Holloway I, Galvin K. *Qualitative research in nursing and healthcare*: John Wiley & Sons; 2016.
194. Britten N. Qualitative interviews in medical research. *Bmj*. 1995;311(6999):251-3.
195. Creswell JW. *Qualitative inquiry and research design : choosing among five traditions*. Thousand Oaks, Calif.: Sage Publications; 1998.
196. Carter S, Henderson L. Approaches to qualitative data collection in social science. In: Bowling A, Ebrahim S, editors. *Handbook of research methods: Investigation, measurement, and analysis*. Berkshire, England.: Open University Press; 2005. p. 215-29.
197. Caronna CA. Why use qualitative methods to study health care organizations? Insights from multi-level case studies. *The SAGE handbook of qualitative methods in health research*. 2010:71-87.
198. Hoff TJ, Witt LC. Exploring the use of qualitative methods in published health services and management research. *Medical Care Research and Review*. 2000;57(2):139-60.
199. Coulter I, Hilton L, Ryan G, Ellison M, Rhodes H. Trials and tribulations on the road to implementing integrative medicine in a hospital setting. *Health Sociology Review*. 2008;17(4):368-83.
200. McDonald R, Waring J, Harrison S. Rules, safety and the narrativisation of identity: a hospital operating theatre case study. *Sociology of health & illness*. 2006;28(2):178-202.
201. Scott WR, Ruef M, Mendel PJ, Caronna CA. *Institutional change and healthcare organizations: From professional dominance to managed care*: University of Chicago Press; 2000.
202. Swanborn P. *Case study research: What, why and how?*: Sage; 2010.
203. Yvonne Feilzer M. Doing Mixed Methods Research Pragmatically: Implications for the Rediscovery of Pragmatism as a Research Paradigm. *Journal of Mixed Methods Research*. 2010;4(1):6-16.
204. Yin RK. *Case study research: Design and methods*. 3rd ed. Thousand Oaks: CA: Sage; 2003.

205. Barbour RS. *Introducing qualitative research : a student's guide*. 2nd ed. ed. London: Sage; 2013.
206. Kawulich BB. *Participant Observation as a Data Collection Method*. 2005. 2005;6(2).
207. Bowling A. *Research methods in health: investigating health and health services* Maidenhead: Open University Press; 2014.
208. Yin RK. *Discovering the future of the case study. Method in evaluation research*. *Evaluation practice*. 1994;15(3):283-90.
209. Hartley J. *Case study research. Essential guide to qualitative methods in organizational research*. 2004;1:323-33.
210. Harris M. *History and significance of the emic/etic distinction. Annual review of anthropology*. 1976;5(1):329-50.
211. Denzin NK, Lincoln YS. *Strategies of qualitative inquiry*: Sage; 2008.
212. Hsieh HF, Shannon SE. *Three approaches to qualitative content analysis. Qualitative health research*. 2005;15(9):1277-88.
213. Kitzinger J. *Introducing focus groups. BMJ*. 1995;311:299-302.
214. Kitzinger J. *Qualitative research. Introducing focus groups. Bmj*. 1995;311(7000):299-302.
215. Flick U. *Introducing research methodology: A beginner's guide to doing a research project*: Sage; 2015.
216. Koro-Ljungberg M. *Validity and validation in the making in the context of qualitative research. Qualitative health research*. 2008;18(7):983-9.
217. Spradley JP. *Doing participant observation. JP Spradley, Participant observation*. 1980:53-84.
218. Jenner B, Flick U, von Kardoff E, Steinke I. *A companion to qualitative research*: Sage; 2004.
219. Rapley T. *Doing conversation, discourse and document analysis*: Sage; 2008.
220. Miles MB, & Huberman, A. M. . *Qualitative data analysis: An expanded sourcebook.*: Sage; 1994.
221. Hartley J. *Industrial relations and job insecurity: Learning from a case study. Job insecurity Coping with jobs at risk*. 1991:123-50.
222. Crabtree BF, Miller W. *Doing qualitative research*. Second ed. London: Sage; 1999.
223. Glaser BG, Strauss AL. *Discovery of grounded theory: Strategies for qualitative research*: Routledge; 2017.
224. Flyvbjerg B. *Five misunderstandings about case-study research. Qualitative inquiry*. 2006;12(2):219-45.
225. Allison GT, Zelikow P. *Essence of decision: Explaining the Cuban missile crisis*: Little, Brown Boston; 1971.
226. Romzek BS, Dubnick MJ. *Accountability in the public sector: Lessons from the Challenger tragedy. Public administration review*. 1987:227-38.
227. Patrick J. *A Glasgow gang observed*: Neil Wilson Publishing; 2013.
228. Thomas G. *How to do your case study*: Sage; 2015.
229. Flyvbjerg B. *Making social science matter: Why social inquiry fails and how it can succeed again*: Cambridge university press; 2001.
230. Maxwell JA. *Qualitative research design: An interactive approach*: Sage publications; 2012.
231. Ritchie J SL. *Qualitative data analysis for applied policy research*. Bryman A BR, editor. London: Routledge; 1994.

232. McDermind F, Peters K, Jackson D, Daly J. Conducting qualitative research in the context of pre-existing peer and collegial relationships. *Nurse Researcher*. 2013(21):28-33.
233. Galae A. Breaking the barriers of insider research in occupational health and safety. *J Heal Saf Res Pract*. 2009(1):3-12.
234. Burns E, Fenwick J, Schmied V, Sheehan A. Reflexivity in midwifery research: The insider/outsider debate. *Midwifery*. 2012;28(1):52-60.
235. Curtis S, Gesler W, Smith G, Washburn S. Approaches to sampling and case selection in qualitative research: examples in the geography of health. *Social science & medicine*. 2000;50(7):1001-14.
236. Hammersley M, Atkinson P. *Ethnography: Principles in practice*: Routledge; 2007.
237. Bernard. HR. *Research methods in anthropology: Qualitative and quantitative approaches*. Walnut Creek CA: 3rd Alta Mira Press; 2002.
238. Dicicco-Bloom B, Crabtree BF. The qualitative research interview. *Medical education*. 2006;40(4):314-21.
239. Palmer VM. *Field Studies in Sociology: A Student's Manual*: University of Chicago Press; 1928.
240. McDermid F, Peters K, Jackson D, Daly J. Conducting qualitative research in the context of pre-existing peer and collegial relationships. *Nurse researcher*. 2014;21(5):28-33.
241. Aligica PD. Institutional and Stakeholder Mapping: Frameworks for Policy Analysis and Institutional Change. *Public Organization Review*. 2006;6(1):79-90.
242. Newcombe R. From client to project stakeholders: a stakeholder mapping approach. *Construction Management & Economics*. 2003;21(8):841-8.
243. Morse JM. Designing funded qualitative research. In: Norman K, Denzin, Lincoln YS, editors. *Handbook of qualitative research*. 2nd ed. Thousand Oaks, CA: Sage; 1994. p. 220-35.
244. Morse JM. *Determining sample size*. Sage Publications Sage CA: Thousand Oaks, CA; 2000.
245. Creswell JW. *Qualitative inquiry and research design: Choosing among five approaches*: Sage; 2012.
246. Guest G, Bunce A, Johnson L. How many interviews are enough? An experiment with data saturation and variability. *Field methods*. 2006;18(1):59-82.
247. Adler PA. How many qualitative interviews is enough?
http://eprints.ncrm.ac.uk/2273/4/how_many_interviews.pdf National Centre for Research Methods 2012.
248. Ritchie J, Lewis J, Elam G. Designing and selecting samples. In: Ritchie J, Lewis J, editors. *Qualitative research practice*. London: Sage; 2003.
249. Baker SE, Edwards R, Doidge M. How many qualitative interviews is enough?: Expert voices and early career reflections on sampling and cases in qualitative research. 2012.
250. Baker SE, Edwards R. How many qualitative interviews is enough?
http://eprints.ncrm.ac.uk/2273/4/how_many_interviews.pdf National Centre for Research Methods 2012.
251. Merriam SB. *Qualitative research :a guide to design and implementation*. San Francisco, Calif.: Jossey-Bass; 2009.
252. Team BLaG. *The review and refresh of Bioscience 2015 : A report to government by the bioscience innovation and growth team*2009.
253. Sciences AoM. *Reaping the rewards : a vision for UK medical sciences*2010.

254. Domain NEPS. Never Events List 2015/16. In: Agency NPS, editor. Skipton House, London: NHS England; 2015.
255. Nicolini D, Waring J, Mengis J. The challenges of undertaking root cause analysis in health care: a qualitative study. *Journal of health services research & policy*. 2011;16 Suppl 1:34-41.
256. Paul JE, Buckley N, McLean RF, Antoni K, Musson D, Kampf M, et al. Hamilton acute pain service safety study: using root cause analysis to reduce the incidence of adverse events. *Anesthesiology*. 2014;120(1):97-109.
257. Ōno T. Toyota production system: beyond large-scale production: Productivity press; 1988.
258. Marshall C, Rossman GB. *Designing Qualitative Research*: SAGE Publications; 1999.
259. Merriam SB, Tisdell EJ. *Qualitative Research: A Guide to Design and Implementation*: Wiley; 2015.
260. Shenton AK. Strategies for ensuring trustworthiness in qualitative research projects. *Education for Information*. 2004;22:63–75
261. Fusch PI, Ness LR. Are we there yet? Data saturation in qualitative research. *The Qualitative Report*. 2015;20(9):1408.
262. Landau D, Drori I. Narratives as sensemaking accounts: the case of an R&D laboratory. *Journal of Organizational Change Management*. 2008;21(6):701-20.
263. Kuper A, Lingard L, Levinson W. Critically appraising qualitative research. *Bmj*. 2008;337.
264. Gale N, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Medical Research Methodology*. 2013;13(1):117.
265. Ritchie J, Spencer L. Qualitative data analysis for applied policy research. In: Bryman, Burgess, editors. *Analysing Qualitative Data*. London: Routledge; 1994. p. 173-94.
266. Smith J, Firth J. Qualitative data analysis: the framework approach. *Nurse Res*. 2011;18(2):52-62.
267. Thurmond VA. The point of triangulation. *Journal of nursing scholarship*. 2001;33(3):253-8.
268. Denzin NKL, Yvonna S. . *Handbook of qualitative research*. Thousand Oaks, CA, US: Sage Publications; 1994. p. 500-15.
269. Merriam S. What Can You Tell From An N of 1?: Issues of validity and reliability in qualitative research. *PAACE Journal of lifelong learning*. 1995;4:50-60.
270. Guba EG. Criteria for assessing the trustworthiness of naturalistic inquiries. *Educational Technology research and development*. 1981;29(2):75-91.
271. Morrow SL. Quality and trustworthiness in qualitative research in counseling psychology. *Journal of counseling psychology*. 2005;52(2):250.
272. Trotter RT. Qualitative research sample design and sample size: Resolving and unresolved issues and inferential imperatives. *Preventive Medicine*. 2012;55(5):398-400.
273. Patton MQ. Enhancing the quality and credibility of qualitative analysis. *Health services research*. 1999;34(5 Pt 2):1189-208.
274. Patton MQ. *Qualitative evaluation and research methods*: SAGE Publications, inc; 1990.
275. Lincoln YS, Guba EG. *Naturalistic inquiry*: Sage; 1985.
276. Morse JM. "Cherry picking": writing from thin data. *Qualitative health research*. 2010;20(1):3.

277. Gold A, Gronewold U, Salterio SE. Error Management in Audit Firms: Error Climate, Type, and Originator. *Accounting Review*. 2014;89(1):303-30.
278. Collins JF, Williford WO, Weiss DG, Bingham SF, Klett CJ. Planning patient recruitment: fantasy and reality. *Statistics in medicine*. 1984;3(4):435-43.
279. Lasagna L. The pharmaceutical revolution forty years later. *Rev Farmacol Clin Exp*. 1984;1:157-61.
280. Gorringe J. Initial preparation for clinical trials. The principles and practice of clinical trials Edinburgh: Livingstone. 1970;4146:38.
281. Agras WS, Bradford RH. Recruitment: an introduction. *Circulation*. 1982;66(6 Pt 2):IV2-5.
282. Lancaster GA. Pilot and feasibility studies come of age! *Pilot and Feasibility Studies*. 2015;1(1):1.
283. Arain M, Campbell MJ, Cooper CL, Lancaster GA. What is a pilot or feasibility study? A review of current practice and editorial policy. *BMC Medical Research Methodology*. 2010;10(1):67.
284. Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, et al. A tutorial on pilot studies: The what, why and How. *BMC Medical Research Methodology*. 2010;10.
285. Wittes J, Brittain E. The role of internal pilot studies in increasing the efficiency of clinical trials. *Statistics in medicine*. 1990;9(1 - 2):65-72.
286. Points to consider when assessing the feasibility of research [Available from: <http://www.ct-toolkit.ac.uk/routemap/feasibility-and-investigator-selection/downloads/AMRC-MCRN-Feasibility-Guide-May2011.pdf>.
287. Horspool MJ, Julious SA, Mooney C, May R, Sully B, Smithson WH. Preventing and Lessening Exacerbations of Asthma in School-aged children Associated with a New Term (PLEASANT): Recruiting Primary Care Research Sites-the PLEASANT experience. *NPJ Prim Care Respir Med*. 2015;25:15066.
288. Reynolds PS, Michael MJ, Spiess BD. Application of Incident Command Structure to clinical trial management in the academic setting: principles and lessons learned. *Trials*. 2017;18(1):62.
289. Kaitin KI e. Protocol design optimization starting to improve study performance. 2014 Contract No.: 5.
290. Selznick P. An approach to a theory of bureaucracy. . *American Sociological Review*. 1943;8(1):47-54.
291. Gehring M, Taylor RS, Mellody M, Casteels B, Piazzzi A, Gensini G, et al. Factors influencing clinical trial site selection in Europe: the Survey of Attitudes towards Trial sites in Europe (the SAT-EU Study). *BMJ open*. 2013;3(11):e002957.
292. Merkus MP, Borgie CAMJd, Haan RJd. Re: Are clinical trials units essential for a successful trial? *Bmj*. 2015(350):h2823.
293. Chalmers I. Regulation of therapeutic research is compromising the interests of patients. *International Journal of Pharmaceutical Medicine*. 2007;21(6):395-404.
294. Levett KM, Roberts CL, Simpson JM, Morris JM. Site-specific predictors of successful recruitment to a perinatal clinical trial. *Clinical trials (London, England)*. 2014;11(5):584-9.
295. The Medicines for Human Use (Clinical Trials) Regulations 2004 [Available from: http://www.legislation.gov.uk/ukxi/2004/1031/pdfs/ukxi_20041031_en.pdf.
296. Food, Administration D. Guidance for industry: oversight of clinical investigations—a risk-based approach to monitoring. 2015.
297. Julie M Bakobaki MR, Nicola Joffe, Sheena McCormack, Sally Stenning, Sarah Meredith. The potential for central monitoring techniques to replace on-site

- monitoring: findings from an international multi-centre clinical trial. *Clinical trials*. 2012;9(2):257-64.
298. Meredith S, Ward M, Booth G, Fisher A, Gamble C, House H, et al. Risk-adapted approaches to the management of clinical trials: guidance from the Department of Health (DH)/Medical Research Council(MRC)/Medicines and Healthcare Products Regulatory Agency (MHRA) Clinical Trials Working Group. *Trials*. 2011;12(1):A39.
 299. Hernandez R, Cooney M, Dualé C, Gálvez M, Gaynor S, Kardos G, et al. Harmonisation of ethics committees' practice in 10 European countries. *Journal of medical ethics*. 2009;35(11):696-700.
 300. van der Wouden JC, Blankenstein AH, Huibers MJ, van der Windt DA, Stalman WA, Verhagen AP. Survey among 78 studies showed that Lasagna's law holds in Dutch primary care research. *J Clin Epidemiol*. 2007;60(8):819-24.
 301. Agency EM. Classification and analysis of the GCP inspection findings of GCP inspections conducted at the request of the CHMP 2014 [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/12/WC500178525.pdf].
 302. Reason J. Managing the management risk: New approaches to organisational safety. *Reliability and Safety in Hazardous Work Systems* Hove, UK: Lawrence Erlbaum Associates. 1993:7-22.
 303. Woods, Johannesen, Cook, Sarter, Dayton. Behind Human Error: Cognitive Systems, Computers and Hindsight. *Crew Systems Ergonomics Information Analysis Center*, Ohio: Univ Research Inst Oh, 1994.
 304. Flyvbjerg B. Survival of the unfittest: why the worst infrastructure gets built—and what we can do about it. *Oxford review of economic policy*. 2009;25(3):344-67.
 305. Kahneman D, and Amos Tversky. . Prospect theory: An analysis of decision under risk. *Econometrica: Journal of the econometric society*. 1979:263-91.
 306. Kahneman D, and Dan Lovallo. Timid choices and bold forecasts: A cognitive perspective on risk taking. *Management Science*. 1993;39(1):17-31.
 307. Lovallo D, and Daniel Kahneman. Delusions of success. *Harvard business review*. 2003;81(7):56-63.
 308. Flyvbjerg B. Curbing Optimism Bias and Strategic Misrepresentation in Planning: Reference Class Forecasting in Practice. *European Planning Studies*. 2007;16(1):3-21.
 309. Dekker S. Just culture: Balancing safety and accountability: CRC Press; 2016.
 310. Reason J. Are we casting the net too widely in our search for the factors contributing to errors and accidents? *Nuclear Safety: A Human Factors Perspective*. 2003:212.
 311. Wachter RM, Pronovost PJ. Balancing “no blame” with accountability in patient safety. *The New England journal of medicine*. 2009;361:1401-6.
 312. Shojania KG, Dixon-Woods M. ‘Bad apples’: time to redefine as a type of systems problem? : BMJ Publishing Group Ltd; 2013.
 313. Dixon-Woods M, Yeung K, Bosk CL. Why is UK medicine no longer a self-regulating profession? The role of scandals involving “bad apple” doctors. *Social science & medicine*. 2011;73(10):1452-9.
 314. Dekker S. The field guide to understanding 'human error': CRC Press; 2017.
 315. Kirk S, Marshall M, Claridge T, Esmail A, Parker D. Evaluating safety culture. *Patient safety: Research into practice*. 2005:173-84.

316. Clarke S. Perceptions of organizational safety: implications for the development of safety culture. *Journal of Organizational Behavior: The International Journal of Industrial, Occupational and Organizational Psychology and Behavior*. 1999;20(2):185-98.
317. Davies HT, Nutley SM, Mannion R. Organisational culture and quality of health care. *BMJ quality & safety*. 2000;9(2):111-9.
318. Edmondson AC. Learning from mistakes is easier said than done: Group and organizational influences on the detection and correction of human error. *The Journal of Applied Behavioral Science*. 2004;40(1):66-90.
319. Michael DN. On learning to plan and planning to learn: The social psychology of changing toward future responsive societal learning 1976.
320. Firth-Cozens J. Cultures for improving patient safety through learning: the role of teamwork. *BMJ quality & safety*. 2001;10(suppl 2):ii26-ii31.
321. Goldacre B. How to get all trials reported: audit, better data, and individual accountability. *PLoS medicine*. 2015;12(4):e1001821.
322. Connelly P. A resource package for CRM developers: Behavioral markers of CRM skill from real world case studies and accidents (Tech. Rep. No. 97-3). Austin: University of Texas, Aerospace Crew Research Project, Department of Psychology. 1997.
323. Weick KE, Sutcliffe KM. Managing the unexpected: Resilient performance in an age of uncertainty: John Wiley & Sons; 2011.
324. Norris B. Human factors and safe patient care. *Journal of nursing management*. 2009;17(2):203-11.
325. Rapala K, Cowan Novak J. Clinical Patient Safety—Achieving High Reliability in a Complex System. *Digital Human Modeling*. 2007:710-6.
326. Berwick LLLDM. 5 years after to Err is Human - What have we learned? *Journal of the American Medical Association*. 2005(293):2384-90.
327. Carthey J, de Leval MR, Wright DJ, Farewell VT, Reason JT. Behavioural markers of surgical excellence. *Safety Science*. 2003;41(5):409-25.
328. Rosenthal MM, Mulcahy L, Lloyd-Bostock S. Medical mishaps: pieces of the puzzle: Open University Press; 1999.
329. Sutcliffe KM, Lewton E, Rosenthal MM. Communication failures: an insidious contributor to medical mishaps. *Academic medicine*. 2004;79(2):186-94.
330. Smith R. Managing the clinical performance of doctors: a coherent response to an intractable problem. *British Medical Journal Publishing Group*; 1999.
331. Gawande A. Education of a knife. *Complications: A surgeon's notes on an imperfect science*. 2002:11-34.
332. Leape LL. Error in medicine. *JAMA : the journal of the American Medical Association*. 1994;272(23):1851-7.
333. McIntyre N, Popper K. The critical attitude in medicine: the need for a new ethics. *British medical journal (Clinical research ed)*. 1983;287(6409):1919.
334. Rosenstein AH, O'Daniel M. Impact and implications of disruptive behavior in the perioperative arena. *Journal of the American College of Surgeons*. 2006;203(1):96-105.
335. Rosenstein AH, O'daniel M. Disruptive Behavior and Clinical Outcomes: Perceptions of Nurses and Physicians: Nurses, physicians, and administrators say that clinicians' disruptive behavior has negative effects on clinical outcomes. *AJN The American Journal of Nursing*. 2005;105(1):54-64.

336. Sydor DT, Bould MD, Naik VN, Burjorjee J, Arzola C, Hayter M, et al. Challenging authority during a life-threatening crisis: the effect of operating theatre hierarchy. *BJA: British Journal of Anaesthesia*. 2013;110(3):463-71.
337. Padmore JS, Jaeger J, Riesenber LA, Karpovich KP, Rosenfeld JC, Patow CA. "Renters" or "owners"? Residents' perceptions and behaviors regarding error reduction in teaching hospitals: a literature review. *Academic Medicine*. 2009;84(12):1765-74.
338. Kobayashi H, Pian-Smith M, Sato M, Sawa R, Takeshita T, Raemer D. A cross-cultural survey of residents' perceived barriers in questioning/challenging authority. *BMJ quality & safety*. 2006;15(4):277-83.
339. Peerally MF, Carr S, Waring J, Dixon-Woods M. The problem with root cause analysis. *BMJ quality & safety*. 2016.
340. Brown DS. Subordinates' views of ineffective executive behavior. *Academy of Management Journal*. 1964;7(4):288-99.
341. Caro F. Approaches to evaluative research: a review. *Human Organization*. 1969;28(2):87-99.
342. Naquin CE, Tynan RO. The team halo effect: Why teams are not blamed for their failures. *Journal of Applied Psychology*. 2003;88(2):332-40.
343. Stake RE. *The art of case study research*: Sage; 1995.
344. Baxter P, Jack S. Qualitative case study methodology: Study design and implementation for novice researchers. *The qualitative report*. 2008;13(4):544-59.
345. Galea A. Breaking the barriers of insider research in occupational health and safety. *Journal of Health & Safety Research & Practice*. 2009;1(1):3-12.
346. O'Donnell D, Porter G, McGuire D, Garavan TN, Heffernan M, Cleary P. Creating intellectual capital: a Habermasian community of practice (CoP) introduction. *Journal of European Industrial Training*. 2003;27(2/3/4):80-7.
347. Johansson R. ON CASE STUDY METHODOLOGY. *Open house international*. 2007;32(3).
348. Becker HS. Problems of inference and proof in participant observation. *American sociological review*. 1958;23(6):652-60.
349. Schwartz MS, Schwartz CG. Problems in participant observation. *American journal of sociology*. 1955;60(4):343-53.
350. Elliott J. Educational research and outsider - insider relations. *International Journal of Qualitative Studies in Education*. 1988;1(2):155-66.
351. Dickson-Swift V, James EL, Kippen S, Liamputtong P. Blurring boundaries in qualitative health research on sensitive topics. *Qualitative health research*. 2006;16(6):853-71.
352. Renzetti CM, Lee RM. *Researching sensitive topics*. 1993.
353. Robertson J. I. *Ethical Issues and Researching Sensitive Topics: Mature Women and Bulimia*. *Feminism & Psychology*. 2000;10(4):531-7.
354. Diller T, Helmrigh G, Dunning S, Cox S, Buchanan A, Shappell S. The Human Factors Analysis Classification System (HFACS) applied to health care. *Am J Med Qual*. 2014;29(3):181-90.
355. Evans SM, Berry J, Smith B, Esterman A, Selim P, O'shaughnessy J, et al. Attitudes and barriers to incident reporting: a collaborative hospital study. *Quality and Safety in Health Care*. 2006;15(1):39-43.
356. Kingston MJ, Evans SM, Smith BJ, Berry JG. Attitudes of doctors and nurses towards incident reporting: a qualitative analysis. *MEDICAL JOURNAL OF AUSTRALIA*. 2004;181:36-9.

357. Peerally MF, Carr S. Longitudinal patient safety education as a means to promote organizational learning in different resource settings. *Medical teacher*. 2016;38(5):532-.
358. Ramanujam R, Goodman PS. The challenge of collective learning from event analysis. *Safety science*. 2011;49(1):83-9.
359. Hettinger AZ, Fairbanks RJ, Hegde S, Rackoff AS, Wreathall J, Lewis VL, et al. An evidence - based toolkit for the development of effective and sustainable root cause analysis system safety solutions. *Journal of Healthcare Risk Management*. 2013;33(2):11-20.
360. Percarpio KB, Watts BV, Weeks WB. The effectiveness of root cause analysis: what does the literature tell us? *The Joint Commission Journal on Quality and Patient Safety*. 2008;34(7):391-8.
361. Trbovich P, Shojania KG. Root-cause analysis: swatting at mosquitoes versus draining the swamp. *BMJ quality & safety*. 2017;26(5):350-3.
362. Bell-Syer SEM, Thorpe LN, Thomas K, MacPherson H. GP participation and recruitment of patients to RCTs: Lessons from trials of acupuncture and exercise for low back pain in primary care. *Evidence-based Complementary and Alternative Medicine*. 2011;2011.
363. Tversky A, Kahneman D. Judgment under uncertainty: Heuristics and biases. Utility, probability, and human decision making: Springer; 1975. p. 141-62.
364. Mays N, Pope C. Qualitative research in health care. Assessing quality in qualitative research. *Bmj*. 2000;320(7226):50-2.
365. Freshwater D, Avis M. Analysing interpretation and reinterpreting analysis: exploring the logic of critical reflection. *Nursing Philosophy*. 2004;5(1):4-11.
366. Gearing RE. Bracketing in research: A typology. *Qualitative health research*. 2004;14(10):1429-52.
367. Gadamer H-G, Weinsheimer J, Marshall DG. *EPZ truth and method*: Bloomsbury Publishing USA; 2004.
368. Nyström M, Dahlberg K. Pre - understanding and openness—a relationship without hope? *Scandinavian Journal of Caring Sciences*. 2001;15(4):339-46.
369. Finlay L. The reflexive journey: mapping multiple routes. *Reflexivity: A practical guide for researchers in health and social sciences*. 2003:3-20.
370. Hinde D. *PRINCE2 Study Guide: 2017 Update*: John Wiley & Sons; 2018.
371. Donaldson MS, Corrigan JM, Kohn LT. *To err is human: building a safer health system*: National Academies Press; 2000.
372. Donaldson LJ, Appleby L, Boyce J. *An organisation with a memory: report of an expert group on learning from adverse events in the NHS*: Stationery Office Norwich, United Kingdom; 2000.
373. Hutchinson A, Young T, Cooper K, McIntosh A, Karnon J, Scobie S, et al. Trends in healthcare incident reporting and relationship to safety and quality data in acute hospitals: results from the National Reporting and Learning System. *BMJ quality & safety*. 2009;18(1):5-10.
374. Graham N. *PRINCE2 for Dummies*: John Wiley & Sons; 2010.
375. Muriana C, Vizzini G. Project risk management: A deterministic quantitative technique for assessment and mitigation. *International Journal of Project Management*. 2017;35(3):320-40.
376. Campbell MK, Claire Snowdon, David Francis, Diana R. Elbourne, Alison M. McDonald, Rosemary C. Knight, Vikki A. Entwistle, Jo Garcia, Ian Roberts, and Adrian M. Grant. . Recruitment to randomised trials: strategies for trial enrolment

and participation study. The STEPS study. Health technology assessment. 2007;11(48):1-123.

Appendix 1

Search Strategy

1. *randomized controlled trials as topic/ or *pragmatic clinical trials as topic/
2. meta analysis.mp.pt. or review.pt. or search:.tw.
3. (MEDLINE or systematic review).tw. or meta analysis.pt.
4. *Randomized Controlled Trials as Topic/mt [Methods]
5. *Randomized Controlled Trials as Topic/
6. "Early Termination of Clinical Trials"/
7. *research design/ or *patient selection/
8. 5 and 7
9. (challenge* or lesson* or barrier* or recruit* or enrolment* or fail* or succe* or unsuccess* or difficult* or problem* or method* or manag*).m_titl.
10. 8 and 9
11. 6 or 10

Data Collection Proforma

Headings:

Setting

What Happened

Research Question

Population/Sampling

Type of Study

Data collection

Methods/Data analysis

Main themes

Main findings

Reasons for Trial Failure

	Strong 2016 (Trials)	Stuart 2015 (Midwifery)	Choi 2016 (Fam/Comm Health)	Keightley 2014 (BDJ)
Setting	Study nested within a feasibility RCT to establish whether a full trial comparing a surgical (oesophagostomy) intervention with a non-surgical (definitive chemotherapy) intervention for localized squamous cell carcinoma (SCC) was viable	The multi-site randomised controlled trial aimed to examine if provision of gFNP (Group Family Nurse Partnership), compared to routine antenatal and postnatal services, could reduce risk factors for child maltreatment. Recruitment fell short and community midwives failed to identify many suitable participants	Parent trial - Church-based cluster randomized clinical trial, 'Better Breast and Cervical Cancer Control for Korean American Women'. Community Health Workers (CHWs) were trained to recruit and retain patients for 6 months. Many delivered intervention (2 hr health literacy education, monthly phone counseling and navigation assistance)	Multicentre paediatric primary dental care randomized controlled trial (FiCTION) failed to recruit.
What happened?	375 patients discussed across 3 centres. 42 eligible. Only 5 randomised. Poor inclusion/recruitment rate	Poor recruitment – fell short of the expected 300 (207) Community midwives only identified 18% of these (originally they were supposed to do all the identification/recruitment) Of these 65 consented to be in the trial	No issues – trial was successful	Trial failed to achieve targets. Study to explore the reasons why and to suggest interventions to improve recruitment
Research question	Study devised to explore the importance of teamwork in recruitment	Study devised to explore barriers to the involvement of community midwives in	The purpose of this study was to explore specific recruitment and retention	Aim was to identify reasons for FiCTION's lower than predicted

	to a multicenter study	identifying potential participants to the above RCT	strategies used by CHWs in a church-based community intervention trial designed to promote breast and cervical cancer screening among KA women	participant recruitment rate and develop practical strategies to support practices in maximising future participant recruitment
Population/sampling	Purposive sampling 21 interviews (8 surgeons – inc. CI and PI, 5 Oncologists – inc PI, 5 Research nurses, 1 Specialist UGI nurse, 1 research fellow, 1 trials coordinator)	13 community midwives interviewed (17 names supplied to researchers)	(out of a total 29 that were involved in parent study and approached) 23 CHWs (distributed between control and intervention churches) in four focus groups of 3-8	39 responses to the web-based survey tool. (13 principal dentists, 4 dentists, 12 dental nurses and 10 practice managers)
Type of study	Qualitative analysis of interview data	Descriptive qualitative investigation using semi-structured audio-recoded interviews	Focus groups moderated by bilingual researcher. Qualitative thematic analysis of audio-recorded/transcribed data	Web based survey tool which consisted of quantitative and qualitative responses.
Data collection	Semi-Structured Topic Guide Face to Face/Telephone	Semi-Structured Face to Face in Community Midwifery offices	X4 focus group sessions	Quantitative survey had 44 questions, qualitative had 5 open questions with free text boxes
Methods (data analysis)	Thematic analysis – Grounded theory Coding frame Data saturation – no new themes emergent	Thematic content analysis (Robson 2011, Silverman 2006) used to identify major themes and subthemes	Thematic analysis (Elo 2008, Kreuger 2009, Stewart 2014)	Quantitative scores aggregated to give scores, and qualitative responses grouped into themes

Main themes	MDT meeting Trial leadership Recruitment process	Issues with midwifery role in trial process Issues with criteria for trial participants Reasons for potential participant refusal Reservations about midwifery care as part of gFNP Views about gFNP programme in the future	(Recruitment strategies) Use of personal network at church Use of formal church network Building on trust and respect Facilitating non-threatening environment (Retention strategies) Trust Realising benefits	(From free text responses) Facilitators to recruitment Barriers to recruitment Suggestions to improve organization of research in general dental practice
Main findings	The importance of the weekly MDT meeting to establish patient eligibility and for building a sense of a 'team' amongst the healthcare professionals was emphasised by team members. Shared leadership models across specialty and professional boundaries appeared to motivate enthusiasm for the study.	Trial had low priority (High clinical workload and depleted workforce) Limited knowledge about intervention Complex eligibility requirements Concern about the quality of the intervention being offered (different from routine midwifery care and delivered by family nurses rather than midwives)	CHWs used themselves as recruitment tools; they effectively used their social networks to provide a non-threatening environment based on the trust relationship they had been building Food may also be a culturally sensitive recruitment promoter for other ethnicities. Use of trust-related retention strategies,	Recruiting paediatric population challenging Few practices had ever participated in research before Practice team did not feel motivated/recognized Training and delegation of tasks through the whole practice team also undertaken by trial team Positive support lacking

	Clinician bias towards the treatment routinely offered by their specialty was perceived by all interviewees.		including good existing relationships	from central trials team – to help with administration and support recruiting teams
?Reasons for trial failure	Clinician bias (Suggest joint MDT meetings) Poor team functioning (interviewees that had worked together for longer were more positive about teams ability to recruit – suggested workshops/teambuilding)	As above: Suggestions included, Sufficient understanding of participant recruitment through increased midwifery education Standardised recordkeeping and dataset to review potential eligibility (currently many databases – increased time and complication) Increased availability of CLRN midwives (research trained and research main priority)	NA	As above – trials team decided to streamline process and to provide administrative support to the practices. Increased number of practices involved so that a higher number of eligible patients could be found. Practices that were successful in recruitment would get gifts (eg. Mugs and teabreak sets)

Appendix 2

Letter of invitation to participate

Dear...

I am a clinical researcher and MD student working at the University of Hull. My supervisor is Professor ***.

As part of the research team that worked on (The Trial), we feel that it is important to look into the reasons why the trial failed.

As you are aware, the trial was foreclosed early by the funder, and the reasons that were cited by (The Funder) was that (The Trial) failed to recruit to target.

As part of this study we aim to undertake a root cause analysis as to why the study failed to recruit and what were the factors that contributed to its early closure.

I attach a copy of the questions that I plan to ask

Participation in this study is completely voluntary, and you are welcome to withdraw at any time.

With your permission, I will audio-record the interview, in order to transcribe this and use it for the purposes of qualitative analysis. The material, and the recording will be

anonymised and stored on a secure NHS computer in the locked trial offices, and all material will be non-attributable to the contributor. Following analysis, this report will form part of my doctoral thesis and any subsequent research publication. All quotes will be anonymised.

If you would like to see a copy of the transcription before any analysis takes place, please let me know.

If you would prefer for the interview not to be audio-recorded, please let me know, and an alternative can be used.

If you have any questions or queries with regards to your contribution, please do not hesitate to contact Professor *** or myself to discuss it.

We hope that by undertaking this assessment of what factors may have contributed to the trial failure, that we will be able to advise and avoid a similar case in the future.

Many thanks for your help.

Appendix 3

Key Statement and Questions

Root Cause Analysis Questionnaire

Reasons why the ** trial closed prematurely

The ** trial closed prematurely, this was due to the withdrawal of funding from the ** (Funder), the reasons that were cited on the formal notice of closure were the failure to meet pre specified targets outlined by the (Funder), which included the number of patients randomised, and the number of actively recruiting centres.

1. What do you think was the major factor that may have played a role in the trial's failure to achieve the specified target?
2. Do you feel that there were specific factors that if changed may have influenced the outcome?
3. Why do you think that the factors mentioned above had such an important influence on the outcome?
4. Is there anything that could have changed in order to prevent the trial outcome?
5. Are there learning points from the experience from ** (The Trial)?
6. How do you feel that the experience from this trial may influence your future research practice?
7. Is there anything that you feel could be done differently in the future?
8. Are there any other points or thoughts you would like to add?

Appendix 4

Example of coding tree

Coding to the Robinson's descriptive framework derived from the risk management literature.

Data from Interview	Memo	Description	Code
<i>The excess treatment costs were perceived to be an issue by many of the organisations and although the NHS is obliged to support research - who pays for that is open to question; so the people taking the view that we must restrict the budgets as much as possible said that they're not paying for this - they would pass the buck around within the organisations, the PCT for example - it was getting such that nobody would sign off the excess treatment costs so that you couldn't get permission to start the trial. So that was the major problem with recruiting the individual centres</i>	Referring to 'changes in regulations' - or certainly changes in bureaucracy - any study being set up at this point of time would have faced very similar challenges - all to do with the research environment at the time	Excess treatment costs	Planning Phase – Internal Risks
<i>What I think was the major problem was the feeling of hopelessness, and the “How can we do this.” What it needed was a bit of management. There was a lack of management...</i>	Lack of presence from the Chief Investigator – lots of other research priorities and competing interests – disengaged trials management team	Investigator suitability	Planning Phase – Internal Risks
<i>I'm not sure, because I'm not clinical - but the PIs were saying - you know - is this clinically even still relevant? That was being muted at the time as well. In</i>	The market potential of the intervention may well have changed - newer drugs on the market may	Market potential	Definition Phase – External Risks

<i>terms of another drug that was also introduced to the market and how that may have had an impact</i>	have made the question less relevant and overall less value for money for the funder		
<i>With the steering committee, I mean you must have seen the Charter- it's meant to provide an independently chaired body which reassures the sponsor and the funder, that the trial is being done properly... and we were sort of in a backwards situation, where (the CI) had written a protocol and submitted it to LREC, had almost started before we had our first trial steering committee. It was quite challenging to explain to him that's not the way the (funding body) work</i>	There did not seem to be the safety procedures - such as the involvement of a committee prior, or involvement of the trials committee. Independently chaired body was unable to fulfil their function or to support the trial.	Planning and Internal processes – critical pathways were not being set	Definition Phase – Internal Risks
<i>Major problem of course of which arose, was that some of the co-applicants, and the trials unit pulling out quite early in the project and again I wasn't party to those reasons, I was just kind of informed, that certain key co-applicants withdrew for - reasons that you'll have to ask other people about. But certainly that would've not helped, cos there was no one to share certain items of the burden with</i>	Key to this was the sudden loss in expertise - this was also covered in the loss of the CTU - neither these co-apps nor the CTU were replaced, or alternative sources of similar expertise sought	Protocol compliance – the protocol was based on having a certain mix of skills and organization involvement	Implementation Phase – Internal Risks
<i>Yes, I think the core team I think didn't believe that actually the HTA targets were immutable targets and I think that that probably contributed to the fact that the targets weren't met because attendance to trying to meet them was left, I think, too late</i>	Did not realise the danger that the trial was in. Relating to the cognizance of the trials management	Compliance – checks on progress were not being made	Implementation Phase – Internal Risks

Appendix 5

CASP appraisal of the study

CASP appraisal tool (10 questions) (2)

- Was there a clear statement of the aims of the research?
- Is a qualitative methodology appropriate?
- Was the research design appropriate to address the aims of the research?
- Was the recruitment strategy appropriate to the aims of the research?
- Was the data collected in a way that addressed the research issue?
- Has the relationship between researcher and participants been adequately considered?
- Have ethical issues been taken into consideration?
- Was the data analysis sufficiently rigorous?
- Is there a clear statement of findings?
- How valuable is the research?

1. Aims of the research:

-Statement of aims of research – please see section *1.4 The research question and objectives*

2. Appropriateness of qualitative methodology

-Justification of qualitative methodology discussed: please see section *5.2.1*

Rationale for using qualitative research methods

3. Appropriateness of research design

- Research approach discussed, appraisal of alternative approaches: please see section 5.3 *Justification of research design*

4. Appropriateness of recruitment strategy

- Recruitment strategy discussed, including purposive sampling and identification of participants: please see section 6.3 *Recruitment* and section 6.4 *Sampling strategy*

5. Appropriateness of data collection

- Data collection methods discussed: please see section 6.6 *Data collection*

6. Consideration of the relationship between researcher and participants

- Discussed in reflexivity sections, including section 1.3 *Research journey and development of research question*, and section 8.5 *Autobiographical reflection*

7. Consideration of ethical issues

- Discussed in section 6.9 *Ethics*

8. Rigor of data analysis

- Discussed in section 6.7 *Data analysis* and section 6.8.1 *Adequacy of data*

9. Clear statement of findings

- Described in *Chapter 7: Findings*, also summarized in section 8.1 *Statement of main findings*

10. Value of the research

- Discussed in section 8.5 *Meaning of the research and implications for stakeholders*