UNIVERSITY OF LIVERPOOL

RECRUITMENT TO RANDOMISED CONTROLLED TRIALS WITH CHILDREN

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ABSTRACT

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Recruitment to randomised controlled trials is known to be difficult. Poor recruitment has several adverse consequences. It affects the validity of study findings, is a common cause of trial extensions and may result in premature termination of trials, which is a huge loss in terms of invested funds, resources and lost knowledge. Non-completion or delayed completion of studies maintains the uncertainty about the efficacy and safety of interventions, thereby delaying or preventing the use of effective interventions and prolonging the use of ineffective or potentially harmful treatments. Recruitment of children to randomised controlled trials is thought to be more challenging due to the vulnerability of the population and the fact that consent is provided by another person usually parents. This thesis aims to review the recruitment performance, i.e. comparison of achieved to anticipated recruitment, of randomised controlled trials with children and identify the factors associated with good or poor recruitment.

We undertook a pilot systematic review of recruitment and retention in randomised controlled trials with children, in published literature, and found that few studies report recruitment information but those that do, report very high rates of percentage total recruitment achieved (%TR) and consent. It was not possible to obtain unbiased estimates of recruitment performance and consent rate due to

the likelihood of selective reporting and/or non-publication of trials with unsuccessful recruitment.

We subsequently conducted a review of recruitment of children to randomised controlled trials in the National Institute of Health Research (NIHR) Clinical Research Network (CRN) portfolio and found that under-recruitment and delayed recruitment are common problems in paediatric trials. Having a trial manager or coordinator was found to be significantly associated with successful recruitment. Other factors such as being an IMP (Investigational Medicinal Product) vs. non-IMP trial, trial of acute vs. chronic illness, having CTU (Clinical Trials Unit) involvement, pilot/feasibility study and additional trial demands had no statistically significant association with recruitment success.

Since recruitment to a clinical trial can be affected by a number of internal and external factors, we conducted a survey with the clinical teams of a multi-centre randomised controlled trial with children, the MAGNETIC trial, to understand the various facilitators and barriers to recruitment. In order to identify the facilitators and barriers to recruitment and establish the recruitment experience of clinical teams in a systematic manner, we developed an evidence based recruitment survey tool. The survey tool is an online questionnaire that presents a comprehensive evidence based list of facilitators and barriers and free text space for responders to record the strategies applied to overcome these barriers and suggestions for change in organisation of trials to boost recruitment.

The survey of clinical teams recruiting to the MAGNETIC trial found that a motivated clinical team with effective communication skills, effective

coordination between study team members at site and between sites and CTU, trial management support, research experience of PI, presence of a research nurse and availability of a designated research team were imperative for trial recruitment success. Heavy clinical workload, shift patterns of work, lack of trained staff particularly out of hours, GCP training, local clinical arrangements and parental anxiety about the safety of experimental treatment were recognised as important barriers to recruitment. A trial specific barrier was difficulty faced by the clinicians in seeking consent from the parents of an acutely ill child in the emergency setting and suggestions were made for consideration of deferred consent.

We concluded that recruitment to randomised controlled trials with children is challenging and poor recruitment and recruitment delays are a common problem. Reporting of recruitment and consent in paediatric trials is poor and needs improvement. Presence of a dedicated trial manager is significantly associated with successful recruitment and the various generic and trial specific facilitators and barriers to recruitment that have been identified can be used by trialists in planning and conducting future clinical trials with children.

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Finally, I thank my family for their constant love and support. I dedicate this thesis to my father.

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ABBREVIATIONS USED IN THIS THESIS

CENTRAL	Cochrane Central Register of Controlled Trials
CI	Chief Investigator
CRN	Clinical Research Network
CTU	Clinical Trials Unit
GCP	Good Clinical Practice
HTA	Health Technology Assessment
ICMJE	International Committee of Medical Journal Editors
IDDM	Insulin Dependent Diabetes Mellitus
IMP	Investigational Medicinal Product
% TR	Percentage total recruitment achieved
PI	Principal Investigator
MCRN	Medicines for Children Research Network
MRC	Medical Research Council
NRES	National Research Ethics Service
NIHR	National Institute of Health Research
NHS	National Health Service
NWHTMR	North West Hub for Trials Methodology Research
RCT	Randomised Controlled Trial

PUBLICATIONS AND PRESENTATIONS ARISING FROM THE WORK IN THIS THESIS

The work contained in Chapter 4 has been published in Trials (Kaur et al 2012). The recruitment survey tool described in this chapter has been adapted for use in Head and Neck cancer trials and is published in BMJ Open (Kaur et al 2013). A poster was presented at the MRC NWHTMR showcase meeting (Liverpool 2011) and annual meeting of the Liverpool Cancer Research UK (Liverpool 2012). The publication has been accessed 4300 times on Bio Med Central site and cited by 17 papers. We have been contacted by four researchers seeking permission to use the survey questionnaire tool.

The work contained in Chapter 3 has been presented (poster presentation) at the 2nd Clinical Trials Methodology Conference (Edinburgh 2013) and the abstract has been published in Trials (Kaur et al 2013).

The work contained in Chapter 5 has been presented at the MRC Hubs for Trials Methodology Research Student Symposium (Manchester 2012) and 2nd Clinical Trials Methodology Conference (Edinburgh 2013). The abstract has been published in Trials (Kaur et al 2013).

A copy of the publications arising from the work in Chapters 3, 4 and 5 is included in Appendix 27.

Chapter 1

INTRODUCTION

1.1 BACKGROUND

High quality clinical research is needed to develop the evidence base required to support decision-making by health care professionals, policymakers and patients. Randomised controlled trials (RCTs) and systematic reviews of RCTs are the 'gold standard' and provide the highest level of evidence for the evaluation of health care technologies. The randomised controlled trial is one of the most powerful study designs that allows a reliable estimate of the effect of an intervention with minimal effect from other factors that could influence the course of the study participants or outcomes (Vader 1998). It has the potential to detect moderate benefits that would otherwise be obscured by bias and random effects (Yusuf, Collins & Peto 1984) and confirm the value of effective treatments and prevent the propagation of worthless treatments (Kerridge, Lowe & Henry 1998). However, successful completion of a randomised controlled trial depends on recruitment of an adequate number of eligible participants in the stipulated time frame and budget.

1.2 RECRUITMENT TO CLINICAL TRIALS

Recruitment to a clinical trial involves enrolment of participants who fulfil the eligibility criteria in accordance with the study protocol (Gul, Ali 2010). Poor recruitment can have several adverse scientific, economic and ethical consequences (Hunninghake, Darby & Probstfield 1987, Watson & Torgerson

2006). Recruitment of a sufficient number of participants is crucial to reach the target sample size so that the study is adequately powered to test the study hypothesis, detect a true treatment effect and avoid a type II error (Drew et al. 2002, Gul, Ali 2010).

Poor recruitment is an important shortcoming that prevents a study from reaching the target sample size (McDonald et al. 2006, Watson & Torgerson 2006, Relton et al. 2010). This limits the statistical power of a study to detect a treatment effect (Altman 1991), thereby reducing the chances of obtaining a statistically significant result when a true difference exists between treatments and decreasing the likelihood of finding evidence of effect for an intervention (Watson & Torgerson 2006, Treweek et al. 2010, Sully, Julious & Nicholl 2013). Slow recruitment results in time or cost extensions thereby increasing the direct and indirect costs of a trial. Poor recruitment may result in premature termination of trials, which is a huge loss in terms of invested funds, resources and lost knowledge. Non-completion or delayed completion of studies maintains the uncertainty about the effectiveness or safety of treatment interventions thereby delaying or preventing the uptake of potentially effective treatments and increasing the risk of people being exposed to ineffective or dangerous treatments (Watson & Torgerson 2006). Studies that terminate prematurely or fail to reach adequate statistical power raise *ethical* concerns as trialists have exposed the participants to an intervention with uncertain benefit and may still be unable to determine whether the intervention does more harm than good at trial completion (Treweek et al. 2010).

Review of existing literature

Recruiting patients to randomised controlled trials is known to be challenging. A review of literature was conducted on Medline and Scopus using the search terms 'recruitment', 'enrolment' combined with the AND connector to search terms 'clinical trials', 'multicentre studies', 'randomised controlled trials' and 'rct' to look for existing evidence on recruitment to clinical trials.

Several studies have examined recruitment to clinical trials from a number of perspectives. There are reviews of literature exploring issues around recruitment and summarising the recruitment experience in clinical trials (Hunninghake, Darby & Probstfield 1987, Lovato et al. 1997); reports of recruitment to specific trials (Vollmer, Hertert & Allison 1992, Childhood Asthma Management Program Research Group 1999, Mihrshashi et al. 2002, Vickers, Meade & Darbyshire 2002, Wynn et al. 2010) and surveys and interviews reporting modifiers and barriers to participation from the health care provider (Hjorth et al. 1996, Goodwin et al. 2000, Maslin-Prothero 2000, Baum 2002, Ehrlich et al. 2002, Spaar et al. 2009). Systematic reviews of literature have identified barriers to participation of patients and clinicians in clinical trials (Prescott et al. 1999, Fayter, McDaid & Eastwood 2007), barriers to recruitment of patients in cancer clinical trials (Tournoux et al. 2006, Mills et al. 2006) and reasons for non-entry of eligible patients into surgical randomised controlled trials (Abraham, Young & Solomon 2006). Systematic reviews have also been conducted to identify strategies for increasing recruitment to randomised controlled trials (Mc Daid et

al. 2006, Judith M Watson and David J Torgerson 2006, Mapstone, Elbourne & Roberts 2007, Caldwell et al. 2010, Treweek et al. 2010).

1.2.1 Magnitude of the problem

Poor recruitment to randomised controlled trials is a widespread problem. Previous studies conducted to assess the extent of the problem indicate that recruitment to randomised controlled trials is difficult. Puffer and Torgerson conducted a survey with the lead authors of individually randomised trials published in the British Medical Journal (BMJ) and Lancet in the years 2000 and 2001. They showed that 51% of multicentre randomised controlled trials reported difficulties with recruitment (Puffer, Torgerson 2003). Haidich and Ioannidis (Haidich, Ioannidis 2001) studied the pattern of enrolment in a cohort of RCTs initiated by the AIDS (Acquired Immunodeficiency Syndrome) Clinical Trials Group between 1986 and 1996 and reported that more than 17% of the included RCTs recruited to less than 50% of target.

An epidemiological review (Campbell et al. 2007) of a cohort of multicentre randomised controlled trials funded by the UK MRC (Medical Research Council) and the UK NHS HTA (National Health Service Health Technology Assessment) program, between January 1994 and December 2002, found that only 38 (31%) of the 114 included trials recruited to 100% of the original target. A further 29 (24%) trials recruited to 80% of target but less than 100%. The recruitment target had to be revised in 42 (34%) trials; of which only 19 (45%) could recruit to 100% of the revised target. Sixty-six (54%) trials requested an extension to the trial grant; a time and cost extension in 42 (64%), time-only extension in 15 (23%) and a cost-

only extension in 8 (12%) trials. The overall start to recruitment was delayed in 47 (41%) trials, early recruitment problems were identified in 77 (63%) and late recruitment problems in 46 (38%) trials.

An update to the review conducted by Campbell et al examined the recruitment performance of multicentre RCTs funded by the UK HTA program and UK MRC between 2002 and 2008 (Sully, Julious & Nicholl 2013). The original target was achieved in 40 (55%) of the 73 included trials, which was a significant improvement compared to trials that recruited between 1994 and 2002 (p-value 0.002). 17 (23%) trials recruited to 80% but less than 100% target. The target had to be revised in significantly fewer numbers of trials, 19% compared to 34% in previous years (p-value 0.036) and 71% of the trials recruited to 100% of the revised target, which was another improvement noted compared to the previous review. An extension was requested in 33 (47%) trials; time-only extension in 22 (30%), time and cost extension in 10 (14%) and cost-only extension in 1 (1%).

These studies indicate an improving trend in recruitment to multicentre RCTs with an increased number of trials recruiting to target and lesser numbers needing revision of target. However, the problem persists and recruitment rates continue to be low with about half the trials failing to meet targets and one-third needing an extension.

1.2.2 Factors affecting recruitment to clinical trials

The factors affecting recruitment to clinical trials can be described as facilitators or barriers from the patients' and health care providers' or clinical teams' perspectives. Prescott et al undertook a systematic review of literature covering

the period from 1986-1996 to determine the factors that limit the quality, number and progress of RCTs. They identified clinician and patient participation as important issues and reported on the barriers to clinician and patient participation in clinical trials (Prescott et al. 1999). Other reviews of literature have reported issues pertaining to participation of physicians and patients in clinical trials (Ellis 2000), and explored the factors that influence participation or non-participation of patients (Cox, McGarry 2003). Fayter et al conducted a systematic review of literature from 1996 to 2004 to identify barriers, modifiers and benefits to cancer trial participation from the health care providers' and patients' perspectives and assessed the included studies for methodological quality (Fayter, McDaid & Eastwood 2007).

Tournoux et al undertook a systematic review of published clinical trials and prospective and retrospective cohort studies up to August 2004 that reported barriers to recruitment of patients to trials in onco-haematology (Tournoux et al. 2006). They identified 75 papers; 33 (44%) reported factors related to patient and 28 (37%) reported clinicians' factors to be important in influencing the inclusion of patients in a clinical trial. 37 (49%) reported influence of other factors such as age of patients, minority populations and advanced stage of disease (30 papers) with the effect of cost of RCTs and influence of an important person and/or legislation reported in 17 papers. Mills et al conducted a systematic review of literature until 2005 to define the nature and extent of barriers identified in quantitative and qualitative studies, which were thought to hinder participation in cancer clinical trials (Mills et al. 2006). Abraham et al systematically reviewed the reasons for non-entry of eligible patients in surgical randomised trials to ascertain

characteristics of eligible patients who are likely to refuse participation and made recommendations to improve recruitment (Abraham, Young & Solomon 2006).

Prescott et al reported the most comprehensive systematic review of barriers to participation by patients and clinical teams in clinical trials of cancer and other illnesses. The findings of other systematic reviews are similar to those described by Prescott et al. Fayter additionally assessed the included studies for methodological quality and found that many studies were of poor quality with threats to internal validity in the form of potential for selection bias, poor reporting of recruitment methods, problems with data collection and lack of reliability and validity of research instrument (Fayter, McDaid & Eastwood 2007).

1.2.2.1 Facilitators for trial participation

Patient perspective

Patient willingness to participate is crucial for successful recruitment to a trial. Several factors have been described that influence a patient's decision to enrol in a clinical trial. The most commonly reported motivator for participation is altruism (Siminoff, Fetting & Abeloff 1989, Larson, McGuire 1990, Lynoe et al. 1991, Newburg, Holland & Pearce 1992, Sutherland et al. 1993, Jensen et al. 1993, Ross, Jeffords & Gold 1994, DeLuca et al. 1995, Slevin et al. 1995, Jenkins, Fallowfield 2000). Benefitting others and contributing to medical knowledge are important reasons mentioned for participating in clinical trials (Cassileth BR, Lusk EJ, Miller DS, Hurwitz S. 1982, Ross, Jeffords & Gold 1994, Slevin et al. 1995, Paskett et al. 1996). However, patients also participate in trials because of the perception that trial participation will be beneficial, will offer better treatment

and provide cure for their ailment (Huizinga et al. 1999, Moritz et al. 2002, Kemeny et al. 2003) and in the hope of receiving extra monitoring, better care and treatment from doctors and nursing staff (Mingus et al. 1996, Schaeffer et al. 1996, Madsen et al. 2002). Patients have been known to participate for reasons of perceived benefit of future generations (Jenkins et al. 1999, Hietanen et al. 2000, Ellis et al. 2001, Madsen et al. 2002), whereas some agree to trial participation to please their physicians (Grunfeld et al. 2002) and to help with a doctor's research (Moritz et al. 2002). Incentives such as compensation for extra expenses related to parking or childcare were found to facilitate participation. Certain demographic characteristics such as being male, an older patient, less educated or from a lower socio-economic background appear to be associated with a greater willingness to participate in randomised clinical trials (Bevan et al. 1993, Henzlova et al. 1994, Verheggen, Nieman & Jonkers 1998). Media coverage and increasing exposure to the internet in recent times has increased patients' awareness about trials and interest in participation. There is evidence that patients are keen to participate and want the option of trial participation to be offered to them (Grunfeld et al. 2002, Shilling et al. 2011).

It is important to bear in mind that literature dating back to 80's and 90's is unlikely to reflect the culture change in recent times; decreased medical paternalism, patients being better informed about their condition and potentially reduced trust in clinicians and health care practitioners. Recent advances in technology and increased access to internet has led to patients being better informed, engaged and empowered for decision-making about participation in clinical trials.

Clinical team perspective

The STEPS study (Campbell et al. 2007) reported case studies of four trials that had recruited successfully and had interesting lessons for recruitment. Interviews were conducted with a range of people with different responsibilities and perspectives to gain role specific and location specific insights into the four included trials. They identified four key stages of a trial that may affect recruitment: *foundation work* involving engagement of collaborators, establishing scientific rigour and funding and financial considerations; *recruitment processes*; *delivery of care* and *delivery of research*. The authors reported common factors in the success of these trials based on analysis of themes identified in these key stages and from the responses of the interviewees. The factors identified by the interviewees for successful recruitment in the different trials were: an important or interesting research question, good trial design, good protocol, clinicians keen to recruit to the trial, drugs tested already so easier to explain to patients, no extra demands on patients, no competing trials for centres/patients, drugs not available outside the trial, excellent trial management, good communication between trial team and clinicians, helpful trials unit, centre accreditation, annual meetings and good public relations. Other factors identified by interviewees were flexibility of trial teams, involvement of GPs in trial design, adequate numbers and willingness of practices to take part, pragmatic study design, good funding, trial teams with good communication and responsiveness to problems, good infrastructure, minimal impact on practice running and costs, minimising work for health professionals, prior screening to ensure patients were eligible, presence of

research nurses and teams working hard at explaining the trial to patients (Campbell et al. 2007).

1.2.2.2 Barriers to trial participation

Patient perspective

Treatment preference for or against a particular treatment was identified as a common reason for declining participation (Spiro et al. 2000, Ringberg, Moller 2000, Fleissig, Jenkins & Fallowfield 2001, Lara et al. 2001, Ellis et al. 2001, Kemeny et al. 2003, Westcombe et al. 2003). Patients have been known to be averse to randomisation and treatment choice by random allocation (Jack, Chetty & Rodger 1990, Llewellyn-Thomas et al. 1991, Schwartz, Fox 1995, Fallowfield et al. 1998, Featherstone, Donovan 1998). Participants worry about experimentation and receiving treatment of unproven efficacy (Tripathy, Patel & Brown 1998, Wiley et al. 1999, Jenkins et al. 1999, Ellis et al. 1999, Kemeny et al. 2003). They have concerns about side effects of treatment and may not want to take an experimental medicine or placebo (Bowen, Hirsch 1992, Stone et al. 1994, Slevin et al. 1995, Yeomans-Kinney et al. 1995). Trials with larger differences in the treatments offered with regards to adverse effects or the possibility of receiving a placebo have been known to experience difficulties with recruitment (Kemp, Skinner & Toms 1984, Yeomans-Kinney et al. 1995, Welton et al. 1999). Additional trial demands such as extra procedures, clinic appointments, in-patient hospital stay and extra travel causing discomfort, inconvenience and additional expense were recognised as barriers (Harth, Thong 1990, Bowen, Hirsch 1992,

Autret et al. 1993, Cunny, Miller 1994, Richardson et al. 1998, Camerini et al. 1999, Maslin-Prothero 2000, Westcombe et al. 2003).

The influence of the physician (Tripathy, Patel & Brown 1998, Richardson et al. 1998, Maslin-Prothero 2000, Westcombe et al. 2003) and family members (Paskett et al. 1996, Motzer, Moseley & Lewis 1997, Tripathy, Patel & Brown 1998, Spiro et al. 2000) was recognised as significant factors affecting trial participation.

Patients' knowledge and understanding

Poor understanding of the rationale for random allocation of treatment (Snowdon, Garcia & Elbourne 1997, Featherstone, Donovan 1998) and lack of knowledge about trial participation (Cunny, Miller 1994) have been acknowledged as major deterrents for patient recruitment. Patients are known to experience problems with the concept of equipoise (Jenkins et al. 1999). Studies show that providing 'enough trial information' (Jenkins, Fallowfield 2000) and informing patients about the treatment arms, equipoise and option of leaving the trial at any time encourages people to be more willing to participate (Fallowfield et al. 1998). However, problems with understanding trial information and 'information overload' have been linked to trial refusal (Stevens, Ahmedzai 2004). Long and complex patient information leaflets have been criticised and the need for simple and easy to understand trial information is well recognised by both patients and practitioners (Shilling et al. 2011).

Clinical team perspective

The clinical teams undoubtedly play a key role in recruitment of participants to a clinical trial. Time constraints have been identified as an important barrier to clinician participation due to heavy clinical workload and managerial responsibilities (Foley, Moertel 1991, Dickinson 1994, Smyth et al. 1994, Aaronson et al. 1996), extra work due to the trial (Hjorth et al. 1996, Fallowfield, Ratcliffe & Souhami 1997) and additional demands of recruitment and follow up in clinical trials (Taylor, Margolese & Soskolne 1984, Taylor 1985, Foley, Moertel 1991, Benson et al. 1991, Langley et al. 2000, Wright et al. 2002, Grunfeld et al. 2002). Other system related barriers are cost of trial participation (Hjorth et al. 1996, Langley et al. 2000), strict timelines and lack of resources. The importance of trial regulation in safeguarding patients has been acknowledged but excessive regulation and unnecessary documentation are regarded as barriers (Grunfeld et al. 2002).

Lack of research experience (Winn et al. 1984, Wadland et al. 1990, Dickinson 1994) and training (Shea et al. 1992), non-availability of additional support staff such as research nurses to help with recruitment (Penn, Steer 1990, Foley, Moertel 1991, Shea et al. 1992, Smyth et al. 1994, Morse et al. 1995) and lack of a stable research team (Henzlova et al. 1994) are thought to hinder recruitment. The importance of infrastructure to support research and appropriate communication between trial organisers and clinicians has been emphasized (Langley et al. 2000). Cook et al highlighted the importance of engaging and motivating all members of the research team involved in recruitment to the trial (Cook, Finlay & Butler-Keating 2002).

The decision by a clinician to not offer a patient the option of participation in a clinical trial is thought to be a major contributory factor to poor accrual (Hunter et al. 1987). A clinician's reluctance to offer participation to a patient may stem due to concerns about side effects of treatment (Winn et al. 1984, Foley, Moertel 1991), additional demands on the patient due to the trial (Siminoff, Fetting & Abeloff 1989, Smyth et al. 1994, Aaronson et al. 1996) and hesitation to enrol severely ill patients (Antman et al. 1985, Aaronson et al. 1996). The potential conflict in their role as a clinician and researcher (Taylor, Kelner 1987, Siminoff, Fetting & Abeloff 1989, Penn, Steer 1990, Taylor 1992), loss of clinical autonomy (Taylor, Margolese & Soskolne 1984, Taylor 1985, Taylor, Kelner 1987, Fisher et al. 1991, Taylor 1992, Taylor et al. 1994), difficulty in admitting that they do not know which treatment was better (Taylor, Margolese & Soskolne 1984, Taylor 1985, Taylor, Kelner 1987, Benson et al. 1991) and fear of the resulting impact on their relationship with patients may prevent clinicians from recruiting patients into trials (Taylor, Margolese & Soskolne 1984, Taylor 1985, Taylor, Kelner 1987, Chang et al. 1990, Tognoni et al. 1991). Many doctors expressed difficulty in acknowledging uncertainty and discussing treatment choices including participation in trials (Benson et al. 1991, Fallowfield, Ratcliffe & Souhami 1997).

Clinicians may have a personal preference for a particular treatment (Siminoff, Fetting & Abeloff 1989, Klein et al. 1995), may be unwilling to recruit to trials with 'no treatment' arm (Fisher et al. 1991), have problems in complying with the research protocol (Hjorth et al. 1996) and may demand pragmatic trials (Siminoff et al. 2000, Baum 2002). They may be less likely to engage with the trial if it is

perceived to be irrelevant to their clinical practice (Skeel, Taylor & Harrington 1998) and are more willing to participate if the research question is felt to be important and likely to enhance existing knowledge (Taylor, Margolese & Soskolne 1984, Tognoni et al. 1991). Seeking an informed consent was thought to be problematic and a hindrance to recruitment due to lack of time and availability of trained staff to obtain consent (Taylor 1985, Langley et al. 1987, Benson et al. 1991).

1.2.3 Association of trial features with recruitment success

Campbell et al (2007) tested the association of pre-specified trial features with recruitment success (≥ 100% of original recruitment target). The pre-specified trial features included simple design, good level of funding, multidisciplinary input, consumer input, intervention available only in the trial, pilot phase, dedicated trial manager, local recruitment coordinators, support from a trials unit, being a cancer trial, being a drug trial and funded by the MRC. They found a marginally statistically significant association with the trial being funded by the MRC (OR 2.31, p-value 0.048), being a cancer trial (OR 2.77, p-value 0.026) and not having local paid coordinators (OR 0.34, p-value 0.017). Paid local recruitment coordinators were expected to boost recruitment but the authors discuss that the apparent negative association may be explained by the confounding effect of other factors such as trial complexity and the years in which these trials were undertaken. Some factors such as intervention being available only in the trial, having a dedicated trial manager and being a drug trial were seen

more commonly in trials that recruited successfully but the confidence intervals were wide and the results were not statistically significant (Campbell et al. 2007).

Sully et al (2013) found that trials funded by the MRC appeared to recruit successfully more often than HTA funded trials (61% vs. 45%) but this was not statistically significant (p-value 0.270). Involvement of a clinical trials unit (CTU) was found to have a positive impact on recruitment; 65% of trials with CTU support recruited successfully compared to 48% with no CTU involvement but this was not statistically significant (p-value 0.235). The clinical area was found to be important with 65% of mental health trials recruiting successfully compared to 23% primary care trials. However, the authors report that the sample sizes in the categories were too small for a meaningful statistical analysis. A small negative effect was noted with planned sample size and studies that planned for 80% power were found to be less likely to recruit successfully than studies that aimed for 90% power (Sully, Julious & Nicholl 2013).

1.2.4 Strategies to improve recruitment

Several studies have tried to identify methods to improve recruitment to clinical trials. Systematic reviews of effectiveness of recruitment interventions in randomised controlled trials have found strategies such as personalised letters, making trial material culturally sensitive, telephonic reminders and monetary incentives to be effective. Trials with an open design appeared to benefit recruitment (Watson, Torgerson 2006). A Cochrane systematic review aiming to quantify the effects of recruitment strategies found telephone reminders to non-responders (OR 1.95, 95% CI 1.04, 3.66), use of opt-out procedures for contacting

trial participants (RR 1.39, 95% CI 1.06, 1.84) and open trial design (RR 1.22, 95% CI 1.09, 1.36) to be effective in increasing recruitment (Treweek et al. 2013). Caldwell et al (2010) found that interventions which increased people's awareness of the health problem being studied along with its impact on their health and increasing people's engagement in the learning process improved recruitment. An interactive computer program (RR 1.48, 95% CI 1.00, 2.18), attendance at an education session (RR 1.14, 95% CI 1.01, 1.28), addition of a health questionnaire (RR 1.37, 95% CI 1.14, 1.66) or a video on the health condition (RR 1.75, 95% CI 1.11, 2.74) and monetary incentives were found to be effective (Caldwell et al. 2010).

With greater access to internet and advances in technology in recent times, the role of social media in recruitment of participants to clinical trials is being increasingly recognised. It has been shown to be a viable recruitment method for clinical research studies (Frandsen et al 2013, Tweet et al 2011). Social intelligence is seen to offer a faster and less expensive way to identify appropriate potential participants. Social media can be effectively used to provide trial information, engage with potential participants and invite active involvement and input into trial design, thereby improving participant experience and reducing barriers to trial participation. Social media can also be used to enhance trial recruitment via online patient communities and support groups and by the use of social networking sites that can match eligible patients to appropriate trials (Thompson 2014, #trial: clinical research in the age of social media, 2014).

1.3 CLINICAL RESEARCH WITH CHILDREN

1.3.1 Need for conducting clinical research with children

Evidence based medicine is fundamental in bringing about significant improvements in clinical care and achieving better health outcomes in children. The importance of conducting well-designed clinical studies in children is well recognised as is the danger in relying on evidence generated from studies conducted in the adult population (Smyth, Weindling 1999, Smyth 2001, Klassen et al. 2008). Clinical trials have been a key tool in bringing about a significant improvement in the care and survival of children particularly in preterm infants (Liggins, Howie 1972, Crowley 2000), children with malignant disease (Chessells 1992) and chronic diseases, such as sickle cell disease (Quinn, Rogers & Buchanan 2004). Clinical trials have played an important role in the development of vaccines (Waddington et al. 2010, Snape et al. 2010) and important treatments that have led to prevention of childhood diseases and reduction in associated morbidity and mortality (MRC Vitamin Study Research Group 1991, Centers for Disease Control and Prevention (CDC) 2004). Smyth highlighted the top ten cited clinical trials in children that have made a huge impact on paediatric practice and benefitted children world-wide (Smyth 2007).

However, it is recognised that fewer, high quality clinical trials are conducted with children as compared to adults. A review of randomised controlled trials with children published in Archives of Diseases in Childhood from January 1982 to December 1996 identified only 249 studies; most of which were single centre studies with approximately half recruiting fewer than 40 children (Campbell,

Surry & Royle 1998). A review of therapeutic paediatric trials worldwide between 1996 and 2002 reported that majority of the trials were single centre (75%) and the number of children recruited to each trial was less than 50 in 38%, between 50 and 100 in 24% and more than 100 in 34% of the included trials (Sammons, Choonara 2005). A review of selected journals found that adult studies were three times more likely to be RCTs than studies recruiting children (Martinez-Castaldi, Silverstein & Bauchner 2008).

There is evidence to show that the gap between the number of adult and paediatric trials is widening. The number of annual adult trials published in high impact journals was found to double from 1985-2004, with no change in the number of paediatric trials (Cohen et al. 2007). Cohen et al examined 43, 326 RCTs with age specific categorisation published in paediatric specialist journals, general internal medicine journals, journals for each specialty and general paediatric journals with highest impact factors. Adult RCTs were found to increase by 90.5 RCTs per year (95% CI 78-103) which was significantly higher than the rise in the number of paediatric RCTs (16.9 per year, 95% CI 12-22) and RCTs involving both children and adults (22.7 RCTs per year, 95% CI 10-35) (Cohen et al. 2010). Rudolf et al (2010) investigated the research evidence that existed to support clinical decisions in community paediatric practice and found that only 40% decisions were based on good quality evidence (Rudolf et al. 1999).

Lack of evidence can result in delay or non-implementation of treatments that are effective and use of therapies that are ineffective or which may even lead to unintended harm (Roberts R, Rodriguez W, Murphy D,Crescenzi T. 2003,

Klassen et al. 2008). In the absence of direct evidence from trials in children, health care providers are forced to extrapolate results from adult studies and base their clinical decisions on research conducted in adults, which is inappropriate. This is because many childhood diseases are different from adult diseases and the effect of treatments in children may be different from that in adults. The pharmacokinetics and pharmacodynamics of drugs vary with age and children metabolise drugs differently from adults (Wilson 1996, Smyth, Weindling 1999, Steinbrook 2002). Certain treatments may not be tolerated, may be unsafe to use or difficult to administer in children.

The majority of the medicines used in children are off-label and unlicensed (Turner et al. 1998, Smyth, Weindling 1999, Conroy et al. 2000, 't Jong et al. 2000). Use of off-label medications may benefit, have no therapeutic effect or may even result in harm. A lack of therapeutic effect or adverse effects may result from use of an inappropriate dose or to a lack of understanding of the drug's pharmacokinetic and pharmacodynamics profile (Roberts, Lipman 2009). Research in children is necessary to ascertain the safety and effectiveness of treatments and for promotion of their health and well-being. Paediatric research also has implications for adult medicine. Many adult diseases are thought to have their origin early in life and research in early childhood may form the basis of preventative strategies to control adult diseases (Smyth, Weindling 1999). It is therefore extremely important to conduct high quality clinical trials with children.

1.3.2 Research infrastructure for clinical research with children

In view of increasing recognition of the need for safe and effective treatments for children, legal provisions and regulations were enforced in the US and Europe. The European Paediatric Regulation came into force on the 26th January 2007. The objective was to improve the health of the children in Europe by facilitating the development and availability of high quality, ethically researched and authorised medicines for children (European Medicines Agency).

In the UK, in preparation for the European Regulation that requires pharmaceutical companies to conduct studies with children and a mandatory Paediatric Investigation Plan (PIP), the Department of Health, England working with the Medicines and Healthcare products Regulatory Agency (MHRA), developed a strategy on Medicines for Children in 2004. This included the development of the National Institute of Health Research (NIHR) Medicines for Children's Research Network (MCRN) in 2005 to facilitate the conduct of randomised controlled trials and other well designed studies of medicines for children in the UK.

1.3.3 Conducting randomised controlled trials with children

Ethical issues

Conducting clinical research with children is fraught with several methodological and ethical challenges (Smyth, Weindling 1999). They are perceived as a vulnerable population (Kipnis 2003) with a need to protect them from potential risks from participation in research and to respect their autonomy by seeking an

informed consent from parents or legal guardians and children themselves, when possible (Code of Human Research Ethics). Historically, children have been excluded from participation in research and deprived of the benefits and resulting advancements in medical knowledge, therefore described as the 'therapeutic orphans' (Shirkey 1968).

However, it is evident that children are not small adults and while it is important to protect them from harm, it is equally important that they receive the best treatments which are based on ethically conducted research in children. The risks of participation should be weighed against the benefits keeping the child's interests above those of society and science (Sammons 2009). The potential risks could be due to physical, emotional and/or psychological harm or discomfort and/or stress resulting due to trial participation and can be immediate or delayed. Issues that are important to consider specifically in clinical trials with children are discomfort, pain, fear, unfamiliar surroundings, separation from parents and effects on developing organs and size or volume of biological samples (American Academy of Paediatrics 2010). The counterpoint to risks is the benefit of trial participation, both for the children participating in research and those who may benefit in the future. A well designed clinical trial should offer the optimum treatment approach with the control arm receiving the current best standard treatment and intervention being as good as or better than standard treatment, as required by the Declaration of Helsinki (World Medical Association). Studies have shown improved survival for all participants in trials, both in the intervention and control arm, which may be attributable to the Hawthorne effect (Smyth, Weindling 1999, Vist et al. 2001). This may also be due to better care and closer

monitoring of trial participants or due to the fact that physicians involved in clinical trials are more likely to incorporate trial findings and published evidence into clinical practice (Ellis et al. 1999).

It is suggested that paediatric trials should be designed by professionals with experience in clinical trials and children's medicines, in consultation with parents and patients from appropriate age groups. Study design should be optimised to answer the research question with the smallest number of patients while making efforts to limit the invasiveness of methods used (Sammons 2009). The General Medical Council advises that risk vs. benefits of participation should be carefully assessed at all stages of a trial and it must be ensured that the 'research is not contrary to the child participant's interests' and 'the potential benefits from the development of treatment and furthering of knowledge must outweigh any foreseeable risks' (Medical Research Council 2004, General Medical Council. 2007).

Informed consent

There are then the issues relating to consent and respecting the autonomy of children. The Nuremberg Code 1947 requires that consent be sought from all participants and the Declaration of Helsinki 2013 allows for proxy consent from parents or legal representatives along with assent from the child. The Royal College of Paediatrics and Child Health states that "where children have 'sufficient understanding and intelligence to understand what is proposed' (Gillick vs. West Norfolk), it is they and not their parents whose consent is required by law" (McIntosh et al. 2000).

Researchers should ensure that parents or legal guardians and children are informed about the nature of the study and given the option to withdraw their child at any stage. The children should be actively included in the decision making process and their assent should be monitored on an on-going basis by sensitive attention to verbal and non-verbal cues (Code of Human Research Ethics). Practical considerations in seeking consent from parents include the level of information provided and the extent to which the information is received and understood by the parents. Another consideration is the setting and available time in which parents take the decision, especially for acutely unwell children (Smyth, Weindling 1999). Concepts such as equipoise and randomisation may be confusing and difficult for parents to understand in stressful circumstances (Modi 1994, Mason 1997, Snowdon, Garcia & Elbourne 1997).

Methodological issues

There are also methodological problems in recruiting children to randomised clinical trials. The population pool is smaller and more heterogeneous as compared to adults and there is a need to study different age groups. The number of children affected by a disease may be too small, making it difficult to recruit an adequate sample size to be able to detect a treatment effect (Smyth, Weindling 1999).

1.4 RECRUITMENT TO RANDOMISED CONTROLLED TRIALS WITH CHILDREN

There is limited research on factors that influence recruitment of children to clinical trials. It is thought to be complex (Walterspiel 1990, Macrae 2009, Chamberlain et al. 2009) and more difficult than recruitment to adult trials (Collet et al. 1991). The issues pertaining to recruitment of children in trials have been described in relation to parents, children, doctors and trial related factors (Caldwell et al. 2004).

1.4.1 Parent factors

The children are considered vulnerable as they cannot consent for themselves and therefore parents are entrusted with the responsibility of providing consent for their children to participate in a clinical trial. A study of parents' attitudes to randomised controlled trials involving children showed that although parents understand the importance of conducting research with children, they feel uncomfortable with the responsibility of taking this decision and some parents acknowledged that they would be more reluctant to consent for their child's participation in a trial than if they were being asked to consent for their own participation (Caldwell, Butow & Craig 2003).

Studies show that parents weigh risks against benefits of trial participation (Zupancic et al. 1997, Tait, Voepel-Lewis & Malviya 2003, Caldwell, Butow & Craig 2003), the perceived benefits being access to new and better treatments, greater access to health care professionals and health information, better care and opportunity to meet others in similar circumstances. Some parents had altruistic

motivation for trial participation whereas some viewed trial participation as a treatment option and a 'source of hope' (Caldwell, Butow & Craig 2003). The major reason for participation cited by parents in another study was to know about their child's illness and to help advance medical knowledge (Rothmier, Lasley & Shapiro 2003). Many parents were found to be willing to enrol their child in a trial that had minimal risk even if it was not directly beneficial to the child (Wendler D 2008). However, parents do worry about the side effects of experimental treatment, the chance of their child being randomised to an ineffective treatment and perceive these as potential risks. An additional consideration is the inconvenience of trial participation resulting from additional blood tests, hospital visits, time demands, travel costs and long waiting periods etc. (Harth, Thong 1995, Zupancic et al. 1997, Langley et al. 1998, Hayman et al. 2001) and this can be a major reason for refusal to participate (Hayman et al. 2001).

A qualitative study exploring parents' and practitioners' experiences of recruitment to a clinical trial reported that parents' decision to participate was influenced by factors such as their child's safety and well-being, potential benefit to their child and family, benefit to others and practical aspects of participation. The prime consideration for them was their child's safety and parents stated that they would not consent if they had doubts about safety of treatment (Shilling et al. 2011).

Focus group discussions with paediatricians identified certain parent characteristics that were associated with greater likelihood of trial participation. Middle class, educated, internet information seekers were thought to be more

likely to participate than people from low socioeconomic, non-English speaking background (Caldwell, Butow & Craig 2002).

1.4.2 Child related factors

Children are thought to view trial participation as a positive experience. The key benefit of participation is to learn more about their disease (Cain, McGuinness 2005) and help other children (Wolthers 2006, Cherrill et al. 2007). Other reasons cited for participation in trials are to advance scientific knowledge, age-appropriate incentives and seeking a fun or unique experience (Johnson et al. 1999). They appreciate simple, easy to use trial documents and the adolescent population are keen to use technology to control their disease. The major motivation for trial participation for children is to help themselves and others and parental influence is not a major factor (Cain, McGuinness 2005). However, not surprisingly they dislike blood tests, needles, dietary restrictions, bad tasting medicines and interruption to their normal routine (Johnson et al. 1999). Cherrill (2007) found that children have an understanding of the risks involved in participation in clinical trials. The most common reasons provided by adolescents for refusal to participate in a study of IDDM therapy were increased clinic visits, increased injections and blood glucose monitoring and transportation difficulties (Tercyak et al. 1998).

1.4.3 Clinical team related factors

Caldwell et al reported that paediatricians acknowledge concerns similar to physician related barriers reported in adult studies, such as time constraints, extra work involved for physicians, lack of resources, financial constraints, concern for

patients and about doctor patient relationship, conflict between clinicians' roles as caregivers and researchers, discomfort with randomisation, personal treatment preference and discomfort with discussions about uncertainty and seeking informed consent (Caldwell, Butow & Craig 2002).

Paediatricians believe that parents are reluctant to enrol children to clinical trials because of parental protectiveness, apprehension about experimentation on children and fear of harming or hurting them. Parents are perceived to lack understanding of concepts such as equipoise, placebo use and random allocation and paediatricians sense fear and mistrust of researchers in parents, which affects their willingness to enrol children in a clinical trial. Paediatricians report difficulty in recruiting to placebo-controlled trials. They felt that parents' decision for trial participation is influenced by their opinion and parents are more willing to participate if the trial was considered to be important either because of media promotion or doctors' recommendation. The severity of the child's condition was also felt to be important; parents of children with a poor prognosis were thought to be less likely to agree to participate except for specialities with a research culture such as paediatric oncology (Caldwell, Butow & Craig 2002).

It is evident that physicians worry about the adverse effects of experimental treatment and additional trial demands on parents and families. Shilling et al highlighted a disparity between parents' willingness to be approached about their children's participation in clinical trials and physicians' discomfort in approaching families for recruiting children into trials (Shilling et al. 2011). Physicians felt anxious about asking parents for trial participation particularly if

the children were severely or critically ill, whereas parents accepted and understood the need for research and did not mind being approached even in the most difficult circumstances, provided it was done in a considerate manner. Parents felt positive about trial discussions and practitioners' communication even if they did not contribute much to these discussions. This study suggested the need for mentoring and support for recruiting practitioners to improve their experience of recruiting children in a trial, particularly for less experienced practitioners and in specialities where families and children are perceived to be particularly vulnerable.

1.4.4 Trial related factors

The trial design of clinical trials with children needs to be acceptable to parents, children and paediatricians to ensure adequate recruitment of participants. Parents prefer superiority trials, and pragmatic trial designs with minimal trial demands such as hospital visits or additional blood tests etc. (Caldwell et al. 2004). The use of placebo is perceived as a barrier to trial participation and its use is considered unethical for life threatening illnesses (Caldwell, Butow & Craig 2002, Caldwell, Butow & Craig 2003). The EU guidance on clinical trials with children states that placebo should not be used in trials with children when this implies that an effective treatment will be withheld (Directive 2001/20/EC of the European Parliament and of the Council 2001). Parents have been found to have a limited understanding of the informed consent process (Harth, Thong 1995, Snowdon, Garcia & Elbourne 1997, van Stuijvenberg et al. 1998, Wiley et al. 1999) and find the consent forms difficult to read and complex (Caldwell, Butow & Craig 2003).

Improving the clarity and readability of the consent forms could help parents' understanding of the process. The length and complexity of patient information leaflets have been found to be damaging to families' understanding and have been criticised by both parents and practitioners (Beardsley, Jefford & Mileshkin 2007, Freer et al. 2009, Shilling et al. 2011).

1.5 GAPS IN EXISTING KNOWLEDGE AND RATIONALE FOR THE RESEARCH DESCRIBED IN THIS THESIS

Recruitment to randomised controlled trials is challenging and a common problem. Under-recruitment is a common cause of delays, increased cost and may result in failure to complete trials. It is important to identify the predictors of good or poor accrual to a clinical trial so that appropriate strategies can be put in place to over-ride these problems and facilitate successful completion of a trial.

Although, a lot is known about recruitment of adults to clinical trials, there is very little knowledge about recruitment of children to clinical trials. It is perceived to have additional challenges but empirical evidence is lacking and the scale and magnitude of the problem is not known. The number of randomised controlled trials with children in previous reviews of recruitment performance (Campbell et al. 2007) was limited to ten; three neonatal and seven paediatric trials. There is limited research on the factors that influence recruitment to randomised clinical trials with children.

With increasing recognition and widespread consensus about the need for clinical trials with children and young people, it is imperative to understand the trends in

recruitment to randomised clinical trials with children and identify the facilitators and barriers to recruitment. This will be helpful in developing effective strategies and channelling resources appropriately to counter the problem of under-recruitment in paediatric research. To the best of our knowledge, there is paucity of data with no quantitative research and published evidence on the extent of the problem in children. The aim of this thesis is to review recruitment to randomised controlled trials with children and identify the factors associated with good or poor recruitment.

1.6 STRUCTURE OF THIS THESIS

The thesis is organised in six chapters. Introduction to the topic, a review of literature and rationale for the research described in the thesis have been presented in this chapter (Chapter 1).

In Chapter 2, a pilot systematic review of recruitment and retention in randomised controlled trials with children in published literature is described. The purpose of this review was to estimate the percentage of target recruitment achieved, consent rate and rate of retention of children in randomised controlled trials and assess the feasibility of obtaining this data from published trial reports.

However, we found that very few studies reported data on recruitment and consent and it was not possible to obtain unbiased estimates of recruitment performance from published trial reports. A review of recruitment to randomised controlled trials with children in the NIHR portfolio was then conducted which is described in Chapter 3. The purpose of this review was to compare achieved to

anticipated recruitment and identify the factors associated with good or poor recruitment.

In Chapter 4, the method of developing a web based recruitment survey tool is described. Since recruitment to a trial is governed by various external and internal influences, understanding the motivators and barriers to recruitment in individual trials can generate useful information that can form the basis of strategies to overcome recruitment problems in future trials. The purpose of this survey tool is to systematically establish and monitor the recruitment experience of clinical teams with regard to the perceived facilitators and barriers to recruitment, to identify strategies applied to overcome the barriers and to obtain suggestions for change in organisation of future trials.

In Chapter 5, a survey of recruitment experience of clinical teams recruiting to a large multicentre randomised controlled trial with children, the MAGNETIC trial is described, using the recruitment survey tool described previously. The purpose of this study was to understand the various facilitators and barriers to recruitment experienced by the clinical teams along with the strategies that were implemented to overcome the hurdles.

The discussion is presented in Chapter 6 which summarises the key findings in relation to the research objectives, describes the contribution to existing literature, implications for practice and future research direction.

Chapter 2

METHODS TO EVALUATE RECRUITMENT AND RETENTION OF CHILDREN IN RANDOMISED CONTROLLED TRIALS IN THE PUBLISHED LITERATURE

2.1 BACKGROUND

The success of a clinical research project depends heavily on the research team's ability to recruit an adequate number of research participants. 'Recruitment' is the act of enlisting people for a cause, which in this context is participation in a research project (SAGE Publications, Haboush 2010). It involves the process of screening and selection of appropriate participants, seeking informed consent for participation and enrolment in the study. 'Retention' refers to the participant remaining in the study until it is completed. Effective recruitment and retention of participants through all stages is essential for successful completion of the trial and generation of valid results.

Poor recruitment and retention of participants in clinical trials are serious methodological concerns. Recruitment and retention of children in clinical trials have additional challenges because of the vulnerable nature of the population and the fact that decision to participate is taken by another person, usually a parent. However, there is a paucity of data for paediatric trials and the scale and magnitude of recruitment and retention problems in trials with children is not clearly known. We planned to conduct a systematic review of recruitment and

retention of children to randomised clinical trials reported in the published literature.

2.2 A PILOT SYSTEMATIC REVIEW OF REC RUITMENT AND RETENTION OF CHILDREN IN RANDOMISED CONTROLLED TRIALS

A pilot study was conducted on a small sample of trial reports published between 2006 and 2010. This was done to assess the feasibility of conducting a systematic review of recruitment, consent and retention of children in randomised controlled trials in the published literature. The trial reports were selected from 2006 onwards as reporting was expected to be better in this period than earlier years.

2.2.1 Aims and objectives

The aims of this pilot study were:

- To estimate the percentage of target recruitment achieved (%TR), consent rate and rate of retention of children in randomised controlled trials
- To review the reporting of flow diagram, sample size calculation, target sample size, number of patients who declined to participate and number included in the analysis of primary outcome
- To assess the feasibility of extracting these data from published trial reports.

2.2.2 Methods

2.2.2.1 Identification of relevant studies

Ten published reports of randomised controlled trials were identified for each year from 2006-2010. This was a sample size of convenience. The trials were identified from the Cochrane Central Register of Controlled Trials (CENTRAL) using a list of random numbers generated through statistical software 'R'.

CENTRAL is a bibliographic database developed by 'The Cochrane Collaboration' and is published as a part of 'The Cochrane Library'. It is considered to be the most comprehensive source of reports of randomised controlled trials. CENTRAL includes records identified through systematic searches of MEDLINE and EMBASE, Specialized Registers maintained by the Cochrane groups and records retrieved through manual searching of journals and conference proceedings to identify all reports of randomised controlled trials and controlled clinical trials (Cochrane Central Register of Controlled Trials).

2.2.2.2 Inclusion and exclusion criteria

Individually randomised controlled trials of any health care intervention, in children up to 18 years of age, were eligible for inclusion in the review. Non-randomised or cluster randomised trials were excluded.

2.2.2.3 Search strategy

The Cochrane Central Register of Controlled Trials was searched for all reports of randomised controlled trials published between January 2006 and December

2010. A ‘Child search filter’ (Boluyt et al. 2008) developed by the Cochrane Child Health Field was used to limit the results to trials with children only. The search strategy is shown in Appendix 1.

2.2.2.4 Selection of studies to be included in the pilot

The titles and abstracts of the identified studies were independently screened for eligibility by two reviewers (GK,MB) and full texts were obtained for all potentially relevant reports. The trials were excluded by mutual agreement; where consensus could not be reached, advice was sought from a senior member of the project team (PW).

2.2.2.5 Data extraction

The data from each trial report was extracted independently by both reviewers, using a standard data extraction form (Appendix 2). Disagreements were resolved by discussion; however, where consensus could not be reached, advice was sought from a senior member of the project team (PW). Where data was missing from the trial reports or not reported clearly, the authors were contacted for obtaining missing information or further clarification.

Data was extracted for:

1. Presence of participant flow diagram
2. Reporting of sample size calculation
3. Target sample size
4. Number of participants randomised
5. Number of participants declining to participate

6. Number of participants analysed for primary outcome variable

2.2.2.6 Outcomes

The outcomes of interest were:

- Percentage of target recruitment achieved (%TR), consent rate and overall retention rate of children in randomised controlled trials included in the review.
- proportion of trials that reported a participant flow diagram, sample size calculation, target sample size, number randomised, number declining to participate and number of participants analysed for primary outcome variable
- proportion of trial reports where it was possible to estimate the percentage of target recruitment achieved, retention rate and consent rate

2.2.2.7 Data analysis

Percentage of target recruitment achieved (%TR) was calculated as below:

Total number randomised/recruitment target x100

Retention rate was calculated as below:

Number included in analysis of primary outcome/number randomised x100

Consent rate was calculated as below:

Numbers giving consent/total approached x100

2.2.2.8 Contact with authors

The lead author was contacted by email if information on the parameters of interest was missing.

2.2.3 Results

2.2.3.1 Selection of eligible studies

The initial search on CENTRAL identified 43,450 reports related to clinical trials involving children from 2006 to 2010. The number of trial reports for each year from 2006-2010 are shown in Table 1. 10 trials were selected randomly from each year resulting in a total of 50 trials. The titles and abstracts of the trial reports were independently screened by each reviewer and one trial report was excluded at this stage. The full text of the article was obtained for the remaining 49 trial reports. 10 further trial reports were excluded by agreement between reviewers.

Table 1: Number of trial reports per year from 2006-2010 identified from CENTRAL

Year	Number of controlled trials
2006	8414
2007	8308
2008	8756
2009	8920
2010	9052

2.2.3.2 Reasons for exclusion

Eleven trials were excluded from the review. Five trials were non-randomised (O'Kearney 2009, Powell 2008 Chen 2008, Knott 2007, Jurg 2006); one was

pseudo-randomised (Boivin 2008); three studies were secondary publications of previously conducted randomised controlled trials (Mamtani 2009, Manger 2008, Bellinger 2007); and the participants were more than 18 years of age in two trials (Ladas 2010, Berrak 2007). The excluded trials are listed and referenced in Appendix 3.

2.2.3.3 Description of included studies

39 trial reports of randomised controlled trials of health care interventions, with children up to 18 years of age, were included in the pilot review. A summary of included studies is presented in Appendix 4.

2.2.3.4 Outcome data

The percentage of target recruitment achieved (%TR), consent rate and retention rate for children in randomised controlled trials included in the review are listed in Table 2. The blank spaces indicate the gaps in information in the trial reports.

Table 2: Reporting of information and rates of recruitment, consent and retention in the included trial reports

Study	Flow diagram	Sample size calculation	Target sample size	Number randomised	Number refusing consent	Number analysed for primary outcome variable	Recruitment rate (%)	Consent rate (%)	Retention rate (%)
Akbay 2010	No	Yes	34	40	-	-	118	-	-
Bojang 2010	Yes	Yes	1009	1200	-	1008	119	-	84
Boots 2010	No	Yes	183	200	-	200	109	-	100
Diez-Domingo 2010	Yes	Yes	452	389	-	374	86	-	96
Okan 2010	No	Yes	108	108	-	107	100	92*	99
Schuttelar 2010	Yes	Yes	160	160	54	152	100	75	95
Swadi 2010	Yes	No	-	22	2	22	-	92	100
Waling 2010	Yes	Yes	82	105	0	66	128	100	63
Zampieri 2010	No	No	-	428	-	428	-	-	100
Bassiouny 2009	Yes	No	-	80	9	75	-	90	94
Berrard 2009	Yes	Yes	124	124	7	124	100	95	100
Gelotte 2009	Yes	Yes	256	318	-	291	124	-	92
Kadan-Lottick 2009	No	Yes**	-	92	52	92	-	64	100
Morita 2009	No	Yes	26	28	-	28	108	-	100
Haas 2009	Yes	Yes	159	160	2	158	101	99	99
Parker 2009	Yes	Yes	60	79	12	70	132	87	89
Turk 2009	Yes	No	-	34	-	24	-	-	71
Beaumont 2008	No	No	-	49	-	-	-	-	-
Greenberg 2008	Yes	Yes	1400	167	-	89	12	-	53

Lee 2008	No	No	-	40	-	40	-	-	100
Lynch 2008	No	Yes	100	101	-	-	101	-	-
Patrizi 2008	No	No	-	60	-	57	-	-	95
Szmuk 2008	No	Yes	200	200	-	200	100	-	100
Channon 2007	Yes	Yes	60	80	43	47	133	65	59
Dewan 2007	No	No	60	80	-	68	133	-	85
Ghazal 2007	No	Yes	194	201	-	201	104	-	100
Lewis 2007	No	No	-	14	-	14	-	-	100
Lottmann 2007	Yes	Yes	180	221		210	123		95
Manzoni 2007	Yes	Yes	354	336	12	322	95	97	96
Millar 2007	No	Yes	181	181	-	179	100	-	99
Ahonen 2006	Yes	Yes	150	147	-	96	98	-	65
Berens 2006	No	No	-	43	-	37	-	-	86
Boo 2006	No	Yes	94	106	6	106	113	95	100
Hayden 2006	Yes	No	-	28	-	26	-	-	93
Ng 2006	No	Yes	48	48	5	48	100	91	100
Luhmann 2006	No	Yes	100	102	-	102	102	-	100
Mathai 2006	No	No	-	104	-	-	-	-	-
Mulenga 2006	Yes	Yes	640	255	-	223	40	-	87
Galli 2006	No	No	-	125	-	125	-	-	100

**Numbers refusing consent not reported, consent rate reported in trial report*

*** This study assessed a subset of patients randomised in a larger trial. A retrospective sample size calculation was reported for the subset.*

Percentage of total recruitment achieved (%TR)

21/26 (81%) trials recruited to or above 100% of the target sample size.

Consent rate

9/13 (69%) trials had consent rates of 90% or more.

Retention rate

25/35 (71%) trials had a retention rate of more than 90%.

2.2.3.4 Reporting of data

A summary of information provided in the included studies: reporting a flow diagram, sample size calculation, target sample size, number randomised, number of participants who refused consent and number included in the analysis of primary outcome variable, is provided in Table 2.

Flow diagram

A flow diagram outlining the progress of participants through the study was reported in 18/39 (46%) of trial reports.

Sample size calculation and target sample size

A prospective sample size calculation was reported in 25/39 (64%) trials. Kadan-Lottick 2009 assessed an outcome in a subset of patients randomised in a larger trial and provided a retrospective sample size calculation for this subset. The target sample size was reported in 26/39 (67%) of trial reports. Dewan 2007 reported the sample size estimate without a power calculation.

Number of randomised patients

39/39 (100%) reports provided information on the number of patients who were randomised to these studies. Lynch 2008 reported the 'numbers completing the study'. This study was excluded from retention statistics since the numbers randomised were not clearly specified. The number of participants randomised and analysed for primary outcome variable in the trial was not reported clearly in another study (Bojang 2010). As per the flow diagram, 1200 participants were screened and 1008 were enrolled. However, text in the results section mentioned that "1200 children were screened and allocated to receive the treatments. 1008, that were enrolled, treated and followed up for at least one visit were included in the primary analysis." For purpose of the our study, the number of participants randomised was taken as 1200 and the numbers retained till the end of follow up for primary outcome data was taken as 1008.

Consent refusals

Information on number of participants who refused consent was provided in 12/39 (31%) studies. Okan 2010 did not provide the number of patients who refused consent but reported the consent rate. One study did not specify the exact number of participants refusing consent but reported the numbers excluded collectively with one reason for exclusion being consent refusal. This study was not included in consent rate calculations (Berens 2006).

Analysis of primary outcome variable

The number of patients included in the analysis of primary outcome variable was reported in 35/39 (90%) studies.

2.2.3.5 Feasibility of calculation of percentage of total recruitment achieved, consent and retention rates

Percentage of total recruitment achieved

The percentage of total recruitment achieved (%TR) could be calculated for 26/39 (67%) studies as the target sample size was reported in 26 studies.

Consent rate

The consent rate could be calculated for 13/39 (33%) studies only as data on number of patients who refused consent was available for 12 studies only and one study reported the consent rate.

Retention rate

The retention rate could be calculated for 35/39 (90%) studies as information on number of patients included in the analysis of primary outcome variable was reported for 35 studies.

2.2.4 Contact with Authors

A summary of missing or unclear information in trial reports and information obtained on contacting authors is presented in Appendix 5.

Target sample size

Information on target sample size was missing in 13 trial reports. Dewan 2007 had provided a target but no sample size calculation. Another author (Manzoni 2007) had reported both a prospective and a retrospective sample size calculation. The authors of these trial reports were contacted. Usable information was obtained

from 4 authors who confirmed that sample size calculations were not done and a sample size of convenience was used. One of these four authors provided a definite target sample size (sample size of convenience) that had been used in the trial. Using this information, recruitment rate could be calculated in 27/39 (69%) trial reports. However, there was no information on target sample size in 12/39 (31%) trial reports. Of the trial reports where recruitment rate could be calculated, 22/27 (81%) had recruitment rates of 100% and above.

Consent Refusal

Contact with authors of the 26 trial reports with missing information on consent refusal resulted in 11 responses. Usable information was obtained from 10 (38%). In one response, the author wanted the query to be sent formally to their ethics committee for review and decision. Of the 10 usable responses, 3 authors gave information on numbers refusing consent and 7 authors confirmed that this information was not recorded at the time.

Using the information obtained from contact with authors, the consent rate could be calculated for 16/39 (41%) trial reports as compared to 13/39 (33%) previously. Information on number of consent refusals was not recorded in 7/39 (18%) trial reports. 12/16 (75%) trials reported a consent rate of 90% and above. All of the three trial reports for which the numbers refusing participation were obtained by contacting the authors, the consent rate was higher than 95%.

Clarification on numbers randomised

Two authors were contacted for clarification on the numbers randomised but they did not respond.

Information on the number included in primary outcome analysis

Information on the number included in the primary outcome analysis was missing from four reports and unclear in two. These six authors were contacted for missing information or clarification of numbers reported, but no responses were received.

2.2.5 Discussion

The results of the pilot study demonstrated that a limited proportion of paediatric trial reports present data on recruitment and consent. Efforts to contact authors of these trial reports did not add much information to existing data. It became evident that this method could not be used to obtain true estimates of recruitment and consent rates of children in randomised controlled trials.

This method had some limitations. Few studies reported the percentage total recruitment achieved and consent rates, but those that did, reported very high rates of recruitment and consent. It was difficult to establish whether the high rates of percentage of total recruitment achieved and consent were representative or a result of selective reporting or non-publication of trials with unsuccessful recruitment. Studies that recruit well and have good consent rates may be more likely to report on the same than studies that have poor recruitment and consent rates. Studies with recruitment problems may be more likely to be terminated prematurely or fail to complete and be published. It was evident that a review of published literature alone would give falsely high rates of recruitment.

2.3 ALTERNATIVE METHOD TO REVIEW RECRUITMENT OF CHILDREN IN PUBLISHED RANDOMISED CONTROLLED TRIALS

We tried to explore other methods to review recruitment of children to randomised clinical trials. Alternative sources for data on target sample size such as trial registers were considered. We planned to compare the target sample size in randomised controlled trials using trial registers as the source to numbers randomised in the trial using published trial reports as the source. However, further exploration revealed that this approach would not be feasible either and had its own set of limitations.

2.3.1 Trial registers as source of data on target sample size

Using trial registers as the source of target sample size, relied on the premise that all trials be registered and report data transparently. The International Committee of Medical Journal editors (ICMJE) introduced the policy on trial registration in 2004 (De Angelis et al. 2004) and stated that all trials that began after July 2005 must register in a public trials registry at or before the onset of enrolment. Trials that began enrolment before this date, must register before Sept 13, 2005 to be considered for publication in ICMJE member journals. ICJME updated their statement in 2007 (Laine et al. 2007) to call for prospective registration of trials. In November 2004, the World Health Organisation (WHO) called for members to *"establish a voluntary platform to link clinical trials registers in order to ensure a single point of access and the unambiguous identification of trials with a view to enhancing access to information by patients, families, patient groups and others"* (World Health Organisation). The World Medical Association announced in the revised Declaration of Helsinki, in 2008, "*Every clinical trial must be registered*

in a publicly accessible database before recruitment of the first subject" (World Medical Association Declaration of Helsinki). The number of trial registrations increased dramatically after these initiatives but there were doubts about universal trial registration and data transparency (Bian, Wu 2010).

A review of reporting of sample size calculation in randomised controlled trials (Charles et al. 2009) found that 53% (113/215) of randomised controlled trials included in their review, reported registration in an online database. In 85% (96/113) of these studies, an expected sample size was mentioned in the online trial register. Of these 85%, the expected sample size matched the target sample size in the published trial reports in only 48% (46/96); the relative difference between sample size mentioned in the trial register and published report exceeding 10% in 18 articles (19%) and 20% in 5 articles (5%).

Contact with researchers undertaking similar work with surgical trials revealed the problem of retrospective registration. Rosenthal et al (2013) compared randomised controlled trial registry entries with published reports in three surgical journals in 2010. They found that 56.9% trials had been registered retrospectively, 33.3% registered during trial conduct and only 9.8% were prospectively registered. However, no discrepancy was found in in target sample size for 72.5% trial reports (Rosenthal, Dwan 2013).

The population of studies in trial registers was expected to be different from the population of studies represented in the published literature. The published literature included studies from all countries and the recruitment issues were anticipated to be different, with recruitment being potentially easier in the developing countries due to factors relating to doctor patient relationships and

patients likely to be less informed and less demanding than patients in the developed world.

2.3.2 Limitations of this approach

From the point of view of adopting this method to review recruitment of children to randomised controlled trials, we realised that there were some major limitations:

1 Trials that registered prospectively and started recruitment after 2007 would not have been completed and published by 2010-2011. Thus, it was not feasible to compare trial registers to published reports to get true estimates of recruitment performance.

2. These reviews indicated that a considerable proportion of trials had been registered retrospectively even in the years 2009 and 2010 and we were likely to face similar problems.

3. Selective reporting of target sample sizes in trial registers could not be ruled out completely.

2.4 CONCLUSION

The pilot review of recruitment, consent and retention demonstrated that reporting of paediatric trials was poor. It was difficult to determine whether the high rates of %TR, consent and retention obtained in the pilot study were valid or whether they occurred as a result of selective reporting within published trials, non-publication of trials with unsuccessful recruitment or a combination of both. Other methods

were considered to review recruitment of children to randomised controlled trials but did not prove to be feasible and had some major drawbacks.

It became evident that we needed a prospective approach to review recruitment of children to randomised controlled trials and an actively monitored, objective source of recruitment targets to assess recruitment performance and compare achieved to target sample size. We then proceeded to plan and conduct a review of recruitment of children to randomised controlled trials in the National Institute of Health Research Clinical Research Network (NIHR CRN) portfolio.

Chapter 3

A REVIEW OF RECRUITMENT OF CHILDREN TO CLINICAL TRIALS ON THE NATIONAL INSTITUTE OF HEALTH RESEARCH CLINICAL RESEARCH NETWORK (NIHR CRN) PORTFOLIO

3.1 BACKGROUND

High quality paediatric research is crucial for improving the clinical care and health outcomes of children. Successful completion of a trial and application of its results in clinical practice depends on recruitment of adequate numbers of eligible participants in a given time frame. Recruitment to randomised controlled trials is known to be difficult and a common problem. Previous reviews of recruitment to a cohort of trials funded by the MRC and HTA (Campbell et al. 2007, Sully, Julious & Nicholl 2013) showed that majority of trials failed to recruit to target with over a half needing trial extensions. However, the number of paediatric trials included in these reviews was limited and the degree and extent of the problem is not clearly known for randomised clinical trials with children. It is of vital importance to study the issues around recruitment of children to clinical trials, so that good quality paediatric clinical research can be carried out to address specific child health needs and paediatric clinical care to be more evidence based.

The pilot study showed that a systematic review of recruitment to randomised controlled trials with children in published literature will not provide accurate estimates of recruitment performance, as discussed in Chapter 2. We then proceeded to undertake a review of recruitment to randomised controlled trials

with children in the National Institute of Health Research (NIHR) Clinical Research Network (CRN) portfolio.

National Institute of Health Research Clinical Research Network (NIHR CRN)

The National Institute of Health Research was established by the Department of Health in 2006, to create a 'world-class health research system' within the National Health Service (NHS), under the 2005 Government strategy: Best Research for Best Health (NIHR Clinical Research Network). It was created with an aim to establish the NHS as an internationally recognised centre of research excellence, by providing 'world class facilities' to 'outstanding individuals', conducting 'leading edge research focussed on the needs of patients and the public' (The National Institute for Health Research).

The NIHR Clinical Research Network (CRN) is the research delivery arm of the NHS, which supports a portfolio of over 5000 clinical research studies. It provides the infrastructure for set up and timely delivery of commercial and non-commercial studies in England. It advises researchers on study feasibility, runs streamlined systems for obtaining NHS permission and provides funding to meet the costs of NHS equipment and facilities used during a study. It provides practical help in identifying and recruiting patients to portfolio studies; monitors the number of patients recruited and offers services to help studies in recruiting to time and target (NIHR Clinical Research Network).

The NIHR CRN comprised of eight clinical research networks prior to April 2014; six topic specific research networks, including Cancer, Dementia and Neurodegenerative Diseases, Diabetes, Medicines for Children, Mental Health

and Stroke; and Primary Care Research Network and Comprehensive Clinical Research Network, covering other disease areas (NIHR CRN). The NIHR Medicines for Children Research Network (MCRN) was established in 2005 to improve the coordination and quality of randomised controlled trials and other well designed studies of medicines for children and adolescents. The NIHR MCRN works in partnership with NIHR CRN. It operates through six local research networks that work in partnership with comprehensive local research networks, thirteen clinical study groups, neonatal network and a coordinating centre that also administers the paediatric (non-medicines) speciality group (NIHR MCRN).

NIHR CRN portfolio

The NIHR CRN portfolio is a collection of studies eligible for consideration for support by the Clinical Research Network in England and consists of randomised controlled trials and other well designed studies. The NIHR CRN portfolio is a part of the UK CRN portfolio and is held on the UK CRN portfolio database along with network portfolios for Northern Ireland, Scotland and Wales.

The portfolio database records the research activity data to facilitate the active management of included studies. Anonymised recruitment data is collected for each participant who is recruited to a study. The collected data includes details on the recruitment site, date of recruitment, whether the participant was 'registered' or 'randomised' based on study type and if the participant was a healthy control or suffering from disease (National Institute of Health Research). The recruitment data is submitted by the study teams on a monthly basis, by uploading an excel spread-sheet in a prescribed format, using a secure online tool. The study teams

are mandated to submit monthly recruitment data, which is a condition for continued support from the Clinical Research Network and inclusion in the NIHR CRN portfolio. The recruitment data are used to monitor the studies to ensure that recruitment targets are met.

We conducted a review of recruitment to randomised controlled trials with children on the NIHR CRN portfolio. The portfolio database provided a comprehensive list of commercial and non-commercial randomised controlled trials conducted with children and a rich source of actively monitored and reported recruitment data. This provided the opportunity to examine recruitment performance of these trials in great detail and to assess the factors that influence the recruitment of children.

3.2 AIMS & OBJECTIVES

The aims and objectives of the review were:

1 To compare achieved to anticipated recruitment in terms of numbers and time frame

2 To identify factors that affect recruitment of children to randomised clinical trials

3.3 METHODS

The trials were identified from the NIHR CRN portfolio database: Medicines for Children Research Network (MCRN) studies, paediatric (non-medicinal) studies adopted by the Comprehensive Clinical Research Network (CCRN) and paediatric oncology studies adopted by the National Cancer Research Network (NCRN).

3.3.1 Inclusion and exclusion criteria

Types of studies

Individually randomised controlled trials with children were selected which started recruiting on or after 01/04/2006 and closed to recruitment by 31/03/2013. This cut-off for start date was selected to coincide with the establishment of the NIHR Medicines for Children's Research Network.

Types of participants

Study participants were children ≤18yrs age. Mixed studies with adults and children as research participants, were excluded.

Types of interventions

Any health care intervention

Exclusion criteria:

Non-randomised and cluster randomised trials were excluded.

3.3.2 Access to information

Formal permission was sought from the NIHR CRN coordinating centre. Reporting request was made to the NIHR CRN and MCRN coordinating centres and study lists and recruitment data were requested. Email correspondence with the NIHR coordinating centre is included in Appendix 6.

3.3.3 Identification of relevant studies

The NIHR CRN coordinating centre were asked for a list of studies and recruitment data for paediatric studies which included studies adopted by the

Medicines for Children's Research Network, Paediatric non-medicines speciality group and paediatric oncology studies adopted by the National Cancer Research Network (NCRN). The format of existing data and changes made to extract relevant data from these reports, for the purpose of this analysis, is described in Appendix 7.

MCRN studies

The studies were identified from the NIHR CRN portfolio database using the 'Topic Study Summary' report May 2013. The following filters were applied in the report:

Main Network or supporting network: Medicines for Children

Randomisation: randomised

Active status: Closed – in follow up

Closed – follow up complete

Actual opening date: April 2006 and beyond

Actual closure date: Up to March 2013

Paediatric Non-medicinal studies

The studies were identified from the study list requested from the NIHR CRN coordinating centre. The following filters were applied in the report:

Shortname: Generic Relevance and Cross Cutting Themes

Randomisation: randomised

Active status: Closed – in follow up

Closed – follow up complete

Actual opening date: April 2006 and beyond

Actual closure date: Up to March 2013

The selected list of studies was cross checked with the NIHR Paediatrics (Non-meds) study information and recruitment report May 2013.

National Cancer Research Network (NCRN) studies

A list of paediatric oncology studies was requested from the NCRN coordinating centre. The following filters were applied:

Subtopic: Paediatric oncology

Randomisation: randomised

Active status: Closed – in follow up

Closed – follow up complete

Actual opening date: April 2006 and beyond

Actual closure date: Up to March 2013

3.3.4 Selection of studies to be included in the review

The studies were included in the review if they met the inclusion criteria. Individually randomised controlled trials of any health care intervention, with

participants 18 years or younger, which started recruiting after 01/04/2006 and closed to recruitment by 31/03/2013, were identified.

After initial identification from the NIHR reports, the randomisation status and age of the participants was checked. The online study details provided on the UKCRN Portfolio were used to verify that the studies were randomised controlled studies and age of the participants were 18 years or younger. Additionally, the Medicines for Children's Research Network coordinating centre was requested for permission to access protocols for identified studies. Protocols for Paediatric non-medicines studies were not available and corresponding study teams were emailed to request for a copy of the study protocol. For international studies, the study start and recruitment closure date were checked on the Clinical Trials Register (ClinicalTrials.gov). Information on inclusion criteria was confirmed from a mixture of sources based on availability; study protocol if available, email confirmation from the Chief Investigator or study co-ordinator, and study details provided on the UKCRN Portfolio.

3.3.5 Data extraction

3.3.5.1 Types of data

Recruitment data

The following recruitment data were extracted:

- Target sample size
- Numbers recruited
- Target recruitment period
- Actual recruitment period

Factors affecting recruitment

Hypotheses of factors to be tested for association with recruitment success in clinical trials with children were generated. The factors were decided *a priori* to avoid being data driven in the exploration of factors and avoid the chance of finding an apparent relationship between variables by chance in absence of a real association.

The factors were limited in number to avoid data dredging and getting spurious results due to multiple testing and showing an association between variables due to random error. It was anticipated that factors affecting recruitment are potentially correlated and a suitably powered multivariable analysis would be required to look for significant associations with recruitment success. It was estimated that the number of randomised controlled trials with children on the portfolio was 150. Assuming a 50% probability of recruitment success (binary outcome), six factors were selected in the *a priori* hypothesis, to achieve an 'event per variable ratio' of 10 or more (Peduzzi 1996).

The hypotheses were guided by a review of existing literature on the subject and selected based on the experience of senior members of the research team. An evidence based list of factors affecting recruitment was made and the factors were selected if they were objective, measurable within the scope of the current review and were either amenable to intervention or useful for trialists to be aware of, in conducting future clinical trials with children. The factors tested for association with recruitment success in previous studies were considered in four categories: nature of participant, nature of intervention, trial management and logistical burden of the trial. Factors to be tested in this review were selected from these

categories and clear operational definitions were assigned in advance. The six hypotheses are listed below:

1. *'IMP (Investigational medicinal product) trials recruit better than non-IMP trials.*

IMP trial was defined as 'any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and /or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study the absorption, distribution, metabolism and excretion of one or more investigational medicinal products with the object of ascertaining its safety and/or efficacy'.

IMP was defined as 'a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form' (Directive 2001/20/EC). The included studies were classified as IMP or non-IMP trial based on this definition.

2. *'Trials of chronic illnesses recruit better than trials of acute illnesses'*

Chronic illness was defined as a condition which usually lasts 6 months or longer, results in the child and family having increased contact with health care services and produces limitation of function, activities or social role and dependency on either medication, special diet, medical technology, assistive device, or personal assistance (Stein, Silver 1999). An acute illness was defined as conditions with an

abrupt onset and/or a short duration. This included acute minor and major illnesses and acute presentation of a new or existing chronic illness (Jones et al. 2010). The included trials were classified into 'acute' and 'chronic' illness categories based on the above definitions. Trials enrolling healthy participants were classified as the 'healthy' category.

3. '*Trials with a pilot phase or feasibility assessment recruit better than trials that do not have a pilot phase or feasibility assessment'*

Pilot phase/feasibility study was defined as elements of any prior assessment to establish potential recruitment to the trial. This could include questionnaires to parents to assess willingness to enrol in the trial, assessments of numbers eligible to participate in the study and willing to be randomised, survey of clinician willingness to recruit, establishing the source of patients and choice of recruitment setting, identification of other trials that could potentially compete for patients and/or resources or conducting a miniature version of the trial prior to starting the main study with a view to assess the processes around recruitment.

The trials were classified into three categories- 'yes' 'no' and 'NA' based on if they had a pilot/feasibility assessment prior to starting the trial. The category 'NA' included trials which were pilot studies or feasibility assessments themselves. This information was obtained from the online questionnaire responses from the Chief investigator. The commercial studies were included in the 'yes' category for the purpose of this review, as industry sponsored studies have a feasibility assessment conducted by the companies.

4. *'Trials with CTU (Clinical trials unit) involvement recruit better than trials without CTU involvement*

The trials were classified into two categories, depending on if they had CTU support or not. This was based on information obtained from the Chief Investigators. This analysis was not conducted for commercial studies; as industry sponsored studies have Contract Research Organisations (CROs) and no CTU involvement.

5. *'Trials with a trial manager or coordinator recruit better than trials without a trial manager or coordinator'*

The trials were classified into two categories, based on if it had a trial manager or coordinator. This information was obtained from the Chief Investigators. The commercial studies were considered to have trial manager support as industry led studies have trial management support provided by the CRO.

6. *'Trials with additional trial demands in comparison to standard practice recruit less well than trials without additional trial demands'*

The trials were classified into the following categories, based on additional demand on children, young people and families, resulting due to the trial:

- Additional tests or procedures
- Additional/prolonged hospital/clinic visits or extended hospital stay
- Additional travel distance and/or time and/or associated costs
- Extra days off work, school and/or change in lifestyle of the family
- Extra paperwork for child/young adult and/or family
- None

3.3.5.2 Data sources

3.3.5.2.1. NIHR study reports

Recruitment data were collected from various sources. The study reports obtained from NIHR CRN coordinating centre provided data about

- Global sample size
- Original sample size UK
- Planned sample size UK
- UK recruitment
- Original opening and closing dates
- Planned opening and closing dates
- Actual opening and closing dates

The global sample size was taken as the recruitment target (numbers) for international studies. Original sample size UK reflected the originally planned sample size for studies in the UK, whereas planned sample size reflected the revised sample size. The original sample size UK was taken as the recruitment target (numbers) for UK single and multicentre studies. However, if the revision of target was for reasons other than recruitment difficulties i.e. the drop-out rate was less than expected, the planned sample size was accepted as target. Each study was considered on a separate case basis, depending on the information available from various sources, as shown in Appendix 8. UK recruitment data was used for UK studies, whereas global targets and recruitment data were used to assess the recruitment performance of international studies. Original opening and

closing dates were used to calculate the target recruitment period and actual opening and closing dates for actual recruitment period.

3.3.5.2.2. Online questionnaire sent to Chief Investigators

The Chief investigator of each included study was sent an online questionnaire enquiring about the study characteristics, recruitment data, logistical burden of the trial, details of Clinical Trials Unit (CTU) involvement and pilot or feasibility assessment, if applicable.

Design

The questionnaire was developed using the online survey software www.surveygizmo.com. In the design stage, comments were sought on the content, from staff in the NIHR MCRN Clinical Trials Unit. The questionnaire content and style was modified after discussions with senior members of the research team. The online version was drafted and tested within the research team before it was piloted with Chief Investigators of two trials. Feedback was sought on the content, time taken and ease of completion.

An initial email with the link to the questionnaire was sent to the Chief Investigators of the trials along with a covering letter. The questionnaire and the covering letter are presented in Appendices 9 and 10 respectively. Three additional email reminders were sent to non-responders. Efforts were also made to contact the Chief Investigators by telephone, if no response was received despite the three additional email reminders.

Content and presentation

The *first section* was designed to elicit information on trial characteristics. The initial questions asked about the name of the trial and the name and role of the responder. These two questions were made compulsory, so the responder had to answer these to move on to the next section. Further questions in this section asked about the randomisation status. The responders were provided options to select if the trial was individually or cluster randomised. An 'other' option was provided with a free text space for details. The survey was designed in a manner that responders who selected 'cluster randomised' were led directly to the end of the questionnaire, whereas responders who selected 'individually randomised' or 'other' were directed to the next page.

The second page of the questionnaire asked about clinical setting of recruitment. A preformed list of options was provided for the responders to select. The survey settings allowed responders to select multiple options, if needed. Responders were then asked if blinding was implemented. The 'yes' responders were provided a list of options to specify who was blinded; the others were directed to the next question. Multiple options could be selected and the 'other' option was given with a textbox for responders to provide details. The next question asked if the primary outcome measure was available from routinely collected data such as patient notes or electronic records. The 'yes' responders were directed to the next section; the 'no' responders were asked about the method of data collection.

The *second section* was designed to gather recruitment data. Information was requested on the total number of participants recruited to the trial, target sample size in originally approved protocol, and if the target was revised during the

course of the trial. Trialists who answered ‘yes’ were asked to provide details of the number of revisions, final recruitment target and reasons for revision. Further questions enquired about the planned duration of recruitment in originally approved protocol and if recruitment to the study was discontinued earlier than planned with reasons, if applicable. The next question asked if a trial extension was requested. The ‘yes’ responders were asked to specify the type of extension request and if it was granted. A free text box was provided for trialists to give additional comments on recruitment to the trial, if applicable.

The *third section* was designed to enquire about the additional burden on trial participants or parents/carers, resulting due to the study, which was outside of routine clinical practice. A preformed list of options was provided. Responders were asked to select single or multiple responses and the ‘none’ and ‘other’ option were provided with free text space for responders to provide specific details, as applicable.

The *fourth section* requested information about Clinical Trials Unit (CTU) support. The initial question asked if the trial had CTU support. The responders who answered ‘yes’ were asked about the name of the CTU and if it was registered with the UK Clinical Research Collaboration (UKCRC). A preformed list of options, was provided to gather information on the nature and degree of support provided by the CTU. The ‘other’ option was given with free text space for responders to give relevant details.

Further questions enquired about trial management. The initial question asked if the trial had a trial coordinator or manager. Details of trial coordinator or manager were sought and if the trial coordinator was full time equivalent or less than full

time. The *final section* was designed to ask if a pilot or feasibility assessment was conducted prior to starting the trial. Questions were designed to gather information on the design, aims and methods of the pilot or feasibility study and if it led to any change in the recruitment target or recruitment strategy.

3.3.5.2.3. UK CRN portfolio

The study details provided in the UK CRN portfolio were used to obtain information on

i. type of intervention: Investigational Medicinal Product (IMP) or non-IMP.
ii. type of participants: acute illness vs. chronic illness vs. healthy participants

3.3.5.2.4 Clinical Trials Register

Global recruitment data was used to analyse the recruitment performance of international studies. The global target sample size was recorded on the NIHR CRN portfolio but no data was available on the global recruitment numbers. This data was accessed from Clinical Trials Registers (Clinicaltrials.gov). The numbers recruited to the trial were obtained from the study details provided on the register and study results, wherever available. The study start date was provided in study details and 'history of changes' section was used to identify the recruitment closure date.

3.3.5.3 Recruitment data from different sources

The recruitment data was obtained from different sources. The target sample size, numbers recruited to the study, planned and actual recruitment period were taken

from the study reports obtained from the NIHR CRN portal. Information on target sample size, numbers recruited and planned recruitment period were also requested from the Chief Investigators.

3.3.5.4 Discrepancies in data

There were a number of discrepancies in recruitment data obtained from the NIHR reports and that obtained from the questionnaires completed by the Chief Investigators and the study teams. Efforts were made to resolve these and the Chief Investigators were emailed to ask about the various discrepancies and the NIHR CRN coordinating centre was contacted. The MCRN coordinating centre was requested for granting access to study protocols to confirm the original sample size. Information from study files was requested to clarify discrepancies in target sample size and numbers recruited to the study.

3.3.5.5 Resolution of discrepancies

Information from the various sources was collated and efforts were made to resolve discrepancies based on all available information. Each study was considered on a separate case basis based on the information available from various sources. A set of decision rules was laid to help in the resolution process. The decision rules are presented in the textbox below.

Textbox 1: Decision rules for resolution of discrepancies

Rule 1: Accept value where two out of three data sources match; if not, accept value provided by CI

Rule 2: Discrepancies clarified with the CI or study team

Rule 3: Accept NIHR data where the CI has not responded

The list of studies with recruitment discrepancies and collated recruitment information from all available sources for UK studies are presented in Appendix 8. The global recruitment data for international studies is presented in Appendix 11.

3.3.6 Data analysis

3.3.6.1 Definition of recruitment success

The primary outcome was 'recruitment success'. A study was classified to have recruited successfully, if the study recruited to or above 100% of the original target. The secondary outcome was 'successful recruitment' if a trial recruited to or above 100% of the original target in a period not exceeding 10% beyond the originally planned recruitment period.

3.3.6.2 Recruitment data

A quantitative assessment of recruitment performance was conducted and the studies were classified as 'successful' or 'unsuccessful' based on definitions described previously. The primary and secondary outcomes could be calculated

for UK based studies but for international studies, only the primary outcome could be calculated as data on planned recruitment period was not available.

3.3.6.3 Factors affecting recruitment

The hypotheses of factors affecting recruitment were tested for association with recruitment success (outcome variable) with the various hypothesised factors being the explanatory variables.

3.3.6.4 Statistical Analysis

The data was extracted from various sources and stored in Microsoft Excel 2010. Analysis was performed using SPSS (version 20). The trial characteristics were summarised in frequency tables. The associations between a-priori factors and recruitment success, was presented in 2x2 tables and chi-square test was applied to determine the statistical level of association.

3.4 RESULTS

3.4.1 Study selection

A total of 159 randomised studies (107 MCRN and 52 Paediatric non-medicines) that started recruiting after April 2006 and completed recruitment by March 2013, were initially identified from the study list requested form NIHR CRN coordinating centre. No randomised controlled trial for children <18 years could be identified from the NCRN portfolio. The list of identified MCRN and Paediatric non-medicines studies are presented in Appendices 12 and 13 respectively.

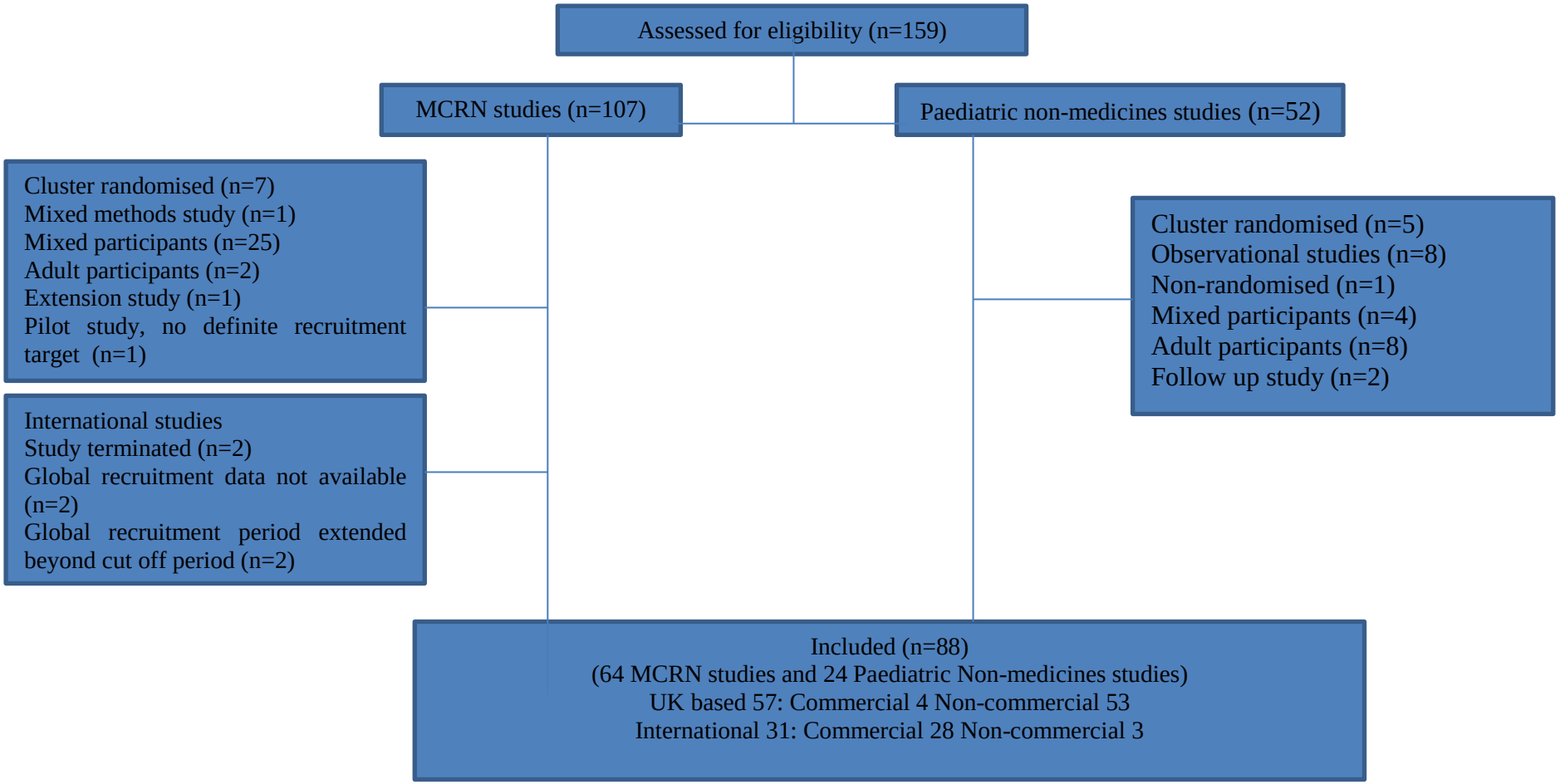
3.4.2 Reasons for exclusion

These studies were then screened for eligibility for inclusion in the review. Non-randomised and cluster randomised studies were excluded. Studies with adult participants were excluded. Mixed studies with children and adults participants were also excluded as separate recruitment targets were not specified for children and it would not have been possible to examine the recruitment of children into these studies. Three MCRN studies were initially included where the upper age limit of participants was higher than 18 years; 19 years in 2 studies and 20 years in 1 study. These studies were included as majority of the population was in the under 18 age group.

75 MCRN and 25 Paediatric non-medicinal studies were found to be eligible for inclusion in the review after initial screening. Recruitment data were extracted from the study reports obtained from the NIHR CRN coordinating centre and online questionnaires were emailed to the Chief investigators of these studies. 4 MCRN and 1 Paediatric non-med studies were identified to be cluster randomised at this stage and excluded from the review. Another MCRN study was excluded at this stage as it was a pilot study with no defined recruitment target number.

Six international MCRN studies had to be excluded; the global recruitment period of two studies extended beyond the census date for inclusion in the review, two studies had been terminated and global recruitment data were not available for two studies. The list of excluded studies with reasons for exclusion is presented in Appendix 14. The number of trials that were identified, excluded and included in the review is presented in the flow diagram below:

Figure 1: Flow Diagram



3.4.3 Included Studies

A total of 88 studies were finally included in the review, 64 of which were MCRN studies and 24 were paediatric non-medicines studies. 57 of the 88 studies were UK based and 31 were international studies. Majority of the UK based studies (93%) were non-commercial and most international studies (90%) were commercial. 72 studies were multicentre, 41 UK based and 31 international. 16 studies were UK single centre studies. A list of included studies with study characteristics is presented in Appendix 15.

3.4.4 Trial characteristics

Information on trial characteristics was obtained through the online questionnaires sent to the Chief investigators. 76 complete and 2 partial responses were included; partial responses with no information and duplicate responses were deleted. The trial characteristics for the 78 trials are described below.

3.4.4.1 Study Design

The study design was 'parallel' in 63 (80.7%) of the 78 studies. Of the 63 studies with a parallel design, 37 (59%) were UK based multicentre studies, 33 non-commercial and 4 commercial. 21 (33%) studies were international studies, 18 commercial and 3 non-commercial and 5 (8%) studies were UK single centre studies. Studies with parallel design were generally interventions for chronic conditions (64%), more commonly medicinal products than non-medicinal interventions.

Six studies had a crossover design. Four studies were UK based non-commercial studies; two single-centre and two multicentre. The other two studies were

international commercial studies. Five of the six studies were of chronic interventions. Two studies had a factorial design and these were UK based single centre, non-commercial studies for chronic interventions. The study design was not described adequately for seven studies.

3.4.4.2 Clinical setting of recruitment

Information on the clinical setting of recruitment was available for 77 studies. 51 (66%) studies recruited from a single clinical setting: 26 from the outpatient clinic, five from the paediatric ward, one from accident & emergency department, nine from intensive care unit, one from postnatal ward, one from general practice, two from community clinics and one from school, three from Child health departments and one from wheel chair services.

19 (25%) studies recruited from multiple clinical settings and seven (9%) studies recruited through other settings. This is presented in Table 3.

Table 3: Clinical Setting of recruitment for included studies

Clinical setting of recruitment	**n**
Single Clinical Setting	**51**
Outpatient clinic	26
Paediatric Ward	5
Accident & Emergency	1
Intensive Care Unit	9
Postnatal ward	1
General practice	1
Community clinic	2
School	1
Clinical research facility	1
Wheelchair services	1
Child Health Departments	3
Multiple Clinical settings	**19**
Outpatient clinic and paediatric Ward	5
Outpatient clinic and community clinic	3
Outpatient clinic, paediatric ward and community clinic	1
Outpatient clinic, accident & emergency and general practice	1
Outpatient clinic, paediatric Ward, accident & emergency, intensive Care Unit, general practice	1
Outpatient clinic, school and contacting help groups	1
Paediatric ward and accident & emergency	2
Paediatric ward and intensive Care Unit	1
Intensive Care Unit and community clinic	1
General practice, community clinic, sure start children's centres and other relevant community venues	1
General practice, clinical research facilities and patients' homes	1
Child Health Departments, media and emails	1
Other settings	**7**
Participant's homes	3
Recruitment via open Exeter database	1
The National Autistic Society (parent referral)	1
Nurseries	1
Help groups	1

3.4.4.3 Blinding

52 (67%) of the 78 included trials observed blinding of one or more of the groups involved and 26 (33%) did not. All the groups were blinded in 17 (33%) studies. Different groups of individuals were blinded in different studies and this is presented in Table 4 below.

Table 4: Blinding in included trials

Blinding	**n (%)**
Yes	52 (59)
No	26 (30)
Missing	10 (11)
Who was Blinded?	**n (%)**
Patients	43 (83)
Health care providers	38 (73)
Patients and health care providers	36 (69)
Data collectors	43 (83)
Outcome adjudicators	32 (62)
Data analysts	28 (54)

3.4.5 Risk factors

3.4.5.1 Investigational Medicinal Product (IMP) vs. non IMP trial

Of the included 88 studies, 61 (69%) were IMP studies and 27 (31%) were non IMP studies. Of the 57 UK studies, 30 (53%) were IMP studies and 27 (47%) were non-IMP studies. All the international studies were IMP studies. The classification of studies is shown in Appendix 16.

3.4.5.2 Acute vs. chronic illness vs. healthy participants

14 (16%) studies were categorised as 'acute', 61 (69%) studies as 'chronic' and 13 (15%) studies enrolled 'healthy' participants. Of the 57 UK studies, 12 (21%) were 'acute', 36 (63%) were 'chronic' and 9 (16%) were in the 'healthy' category. The classification of studies is shown in Appendix 16.

3.4.5.3 Pilot or feasibility assessment

Of the 56 non-commercial studies included in the review, a pilot or feasibility assessment was conducted in 15 (27%) studies, pilot study in 8 and a feasibility assessment in 7 studies. The details of these studies, as described by the trialists are presented in Table 3. 27 (48%) studies had no pilot or feasibility assessment conducted prior to starting the study. 9 (16%) studies were pilot or feasibility studies themselves. This information was not available for 5 (9%) non-commercial studies.

Of the 32 commercial studies, two studies were pilot/feasibility studies themselves. The other 30 commercial studies were included in the 'yes' category for pilot or feasibility assessment, for the purpose of this review, based on the

premise that industry led studies have a feasibility assessment conducted by the pharmaceutical companies. However, being mindful of the fact that feasibility assessment for commercial studies may be different from that conducted in non-commercial studies and that all commercial studies may not have the same level of feasibility assessment, the analysis of association between pilot/feasibility study and recruitment success was conducted both with and without commercial studies to avoid artificial skewing of data (i.e. higher number of studies with a pilot/feasibility assessment) and the possibility of introducing a bias.

Trials that were pilot or feasibility studies themselves were not included in the analysis of association with recruitment success. This analysis was to assess the association between prior pilot or feasibility assessment and potential recruitment to a trial, the hypothesis being that studies with a prior pilot or feasibility assessment were more likely recruit successfully. Therefore, by definition, studies that were pilot/feasibility assessments were excluded.

Table 5: Pilot or feasibility assessment in included studies

Pilot studies
1. Waiting list control study - subjects randomised to active intervention immediately or after 12 months. This design was suboptimal for paediatric population - parents and young people wanted to take part immediately and struggled to commit 12 months in advance. 2. Recruited 30 patients locally to show that parents would consent within the 20 minute time limit and to check that the protocol (especially the administration of the drugs and the outcomes) worked. 3. Design: An open pragmatic study of effectiveness and cost effectiveness of autoinflation for OME. An RCT using telephone randomised allocation and objective outcomes in a pragmatic sample of 28 patients and 4 practices based in Southampton and Oxford areas. Analysis is by child and on and intention to treat basis. 4. The pilot study was an open trial with a small n, to evaluate feasibility and likely success of telephone cognitive behaviour therapy with an adolescent population. Participants with a primary diagnosis of OCD were offered treatment by telephone, and repeated measures were given at fixed time points to evaluate outcome 5. Parallel group double blind RCT to test the impact of slower growth in very early infancy on long-term risk of obesity. 6. Similar design 7. Small open label study of peanut oral immunotherapy to assess safety 8. case-series (N = 8) testing feasibility and acceptability of intervention and measurement
Feasibility assessments
1. We performed two studies - the first to look at safety aspects of potential early discharge and how infants are identified who may deteriorate with bronchiolitis. The second looked at potential reduction in hospital length of stay for helping understand health benefits of the study. 2. Each potential centre was contacted for information on the number of children either commencing or receiving steroids form rheumatic diseases. They were asked on the basis of this data to estimate how many children they felt they could recruit to the POPS study. 3. To determine the feasibility of recruitment and conduct of a community based trial (speaking to parents and staff at local Sure Start Children's Centres) and to determine current levels of dental decay. Focus groups, dental assessment and informal discussions. 4. Pilot RCT to assess feasibility of blinding, recruitment and logistics. 5. Parent questionnaire to assess validity of inclusion criteria (eczema/egg allergy) and willingness to take part in study 6. Assessed numbers of eligible participants across the region over the previous 12 months 7. No details provided

3.4.5.4 CTU involvement

Of the 56 non-commercial studies, 28 (50%) studies had CTU involvement and 23 (41%) did not. This information was not available for 5 (9%) non-commercial studies, all of which were UK based. The commercial studies were excluded from this analysis since industry sponsored studies have Contact Research Organisations (CROs) and no CTU involvement.

The CTU in all the 28 studies were registered with the UK Clinical Research Collaboration (UKCRC). The nature of trial support provided by the CTUs is summarised in Table 6.

Table 5: Nature of support provided by CTU

Nature of support	**n (%)**
Advice on trial design	22 (79)
Costing of the trial and planning of staffing required to develop and manage the trial	18 (64)
Communication with the Clinical Research Networks regarding feasibility and levels of interest	11 (39)
Management of the trial	19 (68)
Liaising with potential centres, identifying and initiating participating centres, and maintaining good communication with each centre	18 (64)
Liaising with potential centres, identifying and initiating participating centres, and maintaining good communication with each centre	11 (39)
Recruiting clinical sites in order to identify and recruit eligible trial patients and allocating a trial entry number and treatment to trial patients	11 (39)
Data management: central coordination and management of essential trial documents and patient data collected from participating clinical sites	25 (89)
Trial monitoring	16 (57)
Conducting interim and final analyses	22 (79)
Others	
Whole trial designed and conducted by OVG	1
Great motivator and moral supporter (a fantastic CTU)	1
Telephone randomisation	1

3.4.5.5 Trial Management

41 of 56 (73%) non-commercial studies had a trial manager but 10 (18%) did not. This information was not available for 5 (9%) non-commercial studies. For the purpose of this analysis, the commercial studies were assumed to have trial management support, as industry led studies have management provided by the CROs. However, keeping in mind that the trial management support for commercial studies may be different from non-commercial studies and that all commercial studies may not have a uniform level of trial management support, analysis for association of recruitment success with presence of a dedicated trial manager was conducted both with and without commercial studies. This was done to avoid the possibility of introducing bias due to an artificial higher number of studies with trial management support.

Details of trial manager or coordinator for the non-commercial studies were present for 40 studies, from the questionnaire received from the Chief Investigators. 15 studies had a professional trial manager; who was full time equivalent in 8 studies. For the remaining seven studies, it was initially 100% and later reduced to 50% in one, variable based on the stage of the trial but overall 70% in another and 40%, 60% and 20% respectively in three others. No information was available for the remaining two trials.

The Chief Investigator provided trial management for four studies, full time equivalent in one, 50% in two and 25% in one. Research fellows were full time equivalent trial managers in five trials. The trial managers were described in the ‘other’ category for the remaining 16 trials and the details are presented in Table 7.

Table 6: 'Other' responses for trial management in non-commercial studies

Trial Manager	Full time equivalent (FTE)		% of FTE
	Yes	No	
Research nurse	1	2	10% 40%
Research associate	1		
Administrative person supported by DRN staff		1	50%
Clinical trial coordinator	1		
Co-applicant		1	
Employed for trial	1	2	80% 50%
Masters graduate	1		
Neurobiologist		1	40-50%
Shared post between research fellow, research nurse and dedicated trial coordinator		1	40%
Trial manager in centre	1		
Senior lecturer		1	10%
Not mentioned		1	40%

3.4.5.6 Additional Trial Demands

The primary outcome measure was available from routinely collected data only in 19 included studies (22%) and other methods of data collection were reported in 59 (67%) studies. No information was available for 10 (11%) studies. Information on additional demands on patient, carer or families due to participation in the trial, was reported for 76 studies. 57 (75%) studies had an additional test or procedure performed as a part of the trial which was outside of routine clinical practice. 35 (49%) studies had an additional and/or prolonged hospital or clinic visit or extended hospital stay. 29 (38%) studies were associated with burden on families resulting due to additional travel distance or time and associated costs. The trial resulted in extra days off work or school and a change in the lifestyle of families in 28 (37%) studies and extra paperwork for the child/young adult and families was noted in 32 (42%) studies. Two trials were associated with no additional trial

demands. The classification of additional trial demands in various categories is shown in Table 8.

Table 7: Additional Trial Demands

Category
Additional tests or procedures 1. Additional painful/invasive procedure for trial that would not happen otherwise 2. Extra blood tests i.e. additional venepuncture event that would otherwise not be necessary 3. Extra blood taken with routine bloods 4. Any other extra tests/procedure
Additional/prolonged hospital/clinic visits or extended hospital stay 5. Additional hospital/clinic visit for protocol defined follow up 6. Prolonged clinic visits 7. Extended hospital stay
Additional travel distance/time and/or associated costs 8. Extra travel cost 9. Extra travel distance/ time
Extra days off work, school and/or change in the lifestyle of the family 10. Extra days off work for family/young adult 11. Extra days off school 12. Change in lifestyle of child/young adult/family
Extra paperwork for child/young adult/family 13. Extra paperwork for child/young adult/family e.g. questionnaires, treatment diaries etc.
None

3.4.6 Outcome data

3.4.6.1 Recruitment success

3.4.6.1.1 Primary outcome

Overall, 61 of 88 (69%) included studies recruited successfully i.e. recruited to 100% target irrespective of time period. Of the 57 UK studies, 36 (63%) recruited successfully.

3.4.6.1.2 Secondary Outcome

20 of 57 (35%) UK studies recruited successfully, i.e. recruited to 100% target in the planned time frame or time period not exceeding 10% of the planned recruitment period. The secondary outcome could be calculated only for the 57 UK studies as global data on planned recruitment period was not available for international studies.

3.4.6.2 Revision of target

The original recruitment target was revised in 13 (23%) UK based studies. The recruitment target was not revised in 39 (68%) studies and this information was not available for five studies. The recruitment target was revised downwards in 12 studies and upwards in 1 study. 11 (85%) studies recruited to 100% of the revised target. The details and reasons for revision of target were provided for 12 studies. The recruitment target was lowered in four studies, in view of trial progress and reduced drop-out rate. Three studies experienced problems with recruitment; recruitment was found to be challenging in two; repeated staff shortages and cancellation of clinics in another study led to loss of patients who had initially

consented to participate in the study. The original recruitment target was arbitrary in one study as no existing data was available to estimate the likely effect size. The target was revised in two studies after interim analysis; a planned reduction in target based on available data in one and adequate numbers recruited for a pilot study in another. One study reported replacing two patients due to not meeting timing of primary endpoint. The recruitment target was revised upwards in one study as the initial powering of the study was reported to be potentially compromised.

Information on recruitment target was available for 24 international studies. The questionnaire requesting study information was not completed by five study teams and information on recruitment target was missing in two responses. Of these 24 studies, information on global recruitment target was provided for 16 studies. The recruitment target had been revised in three studies and all the three studies recruited to 100% of revised target. 13 studies did not need a revision of target.

3.4.6.3 Recruitment discontinued earlier than planned

The recruitment was discontinued earlier than planned in 6 (11%) UK based studies. Of the 6 studies with early discontinuation of recruitment, 4 were due to recruitment difficulties. The results and reasons for early discontinuation of studies are presented in Table 9. Of the 16 international studies with available global recruitment data, the recruitment was discontinued early in one study as recruitment had successfully completed.

Table 8: Recruitment discontinued earlier than planned in included UK based studies

Recruitment discontinued earlier than planned	**n (%)**
Yes	6 (10)
No	46 (81)
Missing	5 (9)
Reasons for early discontinuation	**n**
DMC recommended to the TSC that recruitment should cease because a meta-analysis of the on-going trials showed a highly significant and unexpected difference in mortality	1
Funders not willing to continue	1
Reached recruitment target early	1
Poor recruitment	3

3.4.6.4 Trial extension

A trial extension was requested in 28 (49%) UK based studies. 17 (61%) requests were for a 'no cost extension' and 10 (36%) were for both; 'cost extension' and 'no cost extension'. Information on the type of extension request was not provided for one study. The trial extension was granted in 27 (96%) studies and rejected in only one study. The reasons for requesting trial extension were provided for 27 studies. Each study had multiple reasons for requesting extension and the major themes are summarised below.

20 studies (71%) reported issues with recruitment; a slower than anticipated recruitment rate was reported in twelve studies. Two studies described recruitment difficulties arising due to factors such as changes in prescribing policies, rapid turnover of research nurses, a competing trial and inadequate referral of patients for recruitment to the trial. One study reported staggered recruitment at sites, resulting due to factors such as delays in local R&D approval, NHS structural changes and local staff health issues. Another study mentioned the effect of

seasonal variation; underestimation of recruitment period was described by another. External factors such as H1N1 epidemic and Olympics were reported to affect recruitment in two studies. Three studies also reported a delay in start of the trial. A delay in receiving the Investigational Medicinal Product (IMP) was also reported in one study. Two studies requested for extension to ensure data capture and preparation of materials related to Good Clinical Practice. A time extension was requested in two studies to enable follow up of children, to complete final study visits in one and because of limited capacity to undertake research on the ward in another. One study reported a time extension for a slow early recruitment and a cost extension to support an add-on genetic study.

Of the 16 international studies where information was available on global recruitment targets, one study requested for a 'no cost extension' as the recruitment target had been increased and an additional follow up visit had been added.

3.4.6.5 Association of risk factors with outcome

The a-priori factors were tested for association with recruitment success (primary outcome). Having a trial manager or coordinator was significantly associated with successful recruitment. Other factors such as being an IMP trial, trial of chronic illness, having CTU support, pilot or feasibility assessment and additional trial demands did not show a statistically significant association with successful recruitment. These results are presented in Table 10. The commercial studies were further excluded from analysis of pilot/feasibility assessment and dedicated trial manager, for association with recruitment success, as shown in Table 11.

For UK non-commercial studies, having a trial manager/coordinator showed a statistically significant association with recruitment success (primary outcome). None of the factors were found to be associated with recruitment success (secondary outcome). The results for the association of factors affecting recruitment with recruitment success (primary and secondary outcome) for UK non-commercial studies are presented in Table 12.

Table 9: Association of factors affecting recruitment with recruitment success (primary outcome) for all studies

	Trial with factor that recruited successfully n (%)	p-value
Type of trial		
IMP	44/61 (72.1)	0.390
nonIMP	17/27 (63)	
Type of illness		
Acute	8/14 (57.1)	0.548
Chronic	44/61 (72.1)	
Healthy	9/13 (69.2)	
Pilot/Feasibility assessment prior to main trial*		
Yes	37/45 (82.2)	0.068
No	17/27 (63)	
Missing	5	
CTU involvement**		
Yes	20/28 (71.4)	0.634
No	15/23 (65.2)	
Missing	5	
Trial Management		
Dedicated Trial manager	56/73 (76.7)	0.015
No Dedicated trial manager	4/10 (40)	
Missing	5	
Additional Trial Demand		
Routine data collection for primary outcome***		
Yes	15/19 (78.9)	0.426
No	41/59 (69.5)	
Missing	10	
Additional test or procedure		
Yes	43/57 (75.4)	0.144
No	11/19 (57.9)	
Missing	12	
Additional/prolonged hospital/clinic visit or extended hospital stay		
Yes	24/35 (68.6)	0.659
No	30/41 (73.2)	
Missing	12	
Additional travel distance/time and/or associated costs		
Yes	21/29 (72.4)	0.837
No	33/47 (70.2)	
Missing	12	
Extra days off work/school and/or change in lifestyle of the family		
Yes	21/28 (75)	0.562
No	33/48 (68.8)	
Missing	12	
Extra paperwork for child/young adult/family		
Yes	24/32 (75)	0.518
No	30/44 (68.2)	
Missing	12	

*11 studies were pilot/feasibility studies, **32 commercial studies excluded from analysis of this factor, ***n=78, 2 partial responses included in this analysis

Table 10: Association of factors affecting recruitment with recruitment success for non-commercial studies

	Trial with factor that recruited successfully n (%)	**p-value**
Pilot/Feasibility assessment prior to main trial*		
Yes	13/15 (86.6)	0.103
No	17/27 (62.9)	
Missing	5	
Trial Management		
Dedicated Trial manager	31/41 (75.6)	0.03
No Dedicated trial manager	4/10 (40)	
Missing	5	

*9 studies were pilot/feasibility studies

Table 11: Association of factors affecting recruitment with recruitment success for UK non-commercial studies

	Trial with factor that recruited successfully (PO)* n (%)	p-value	Trial with factor that recruited successfully (SO)* n (%)	p-value
Type of trial				
IMP	16/26 (61.5)	0.915	9/26 (34.6)	0.992
nonIMP	17/27 (63.0)		9/27 (33.3)	
Type of illness				
Acute	6/12 (50.0)	0.478	3/12 (25.0)	0.069
Chronic	23/36 (63.9)		11/36 (30.6)	
Healthy	4/5 (80)		4/5 (80.0)	
Pilot/Feasibility prior to main trial**				
Yes	13/15 (86.7)	0.062	5/15 (33.3)	0.603
No	14/24 (58.3)		10/24 (41.7)	
Missing	5		5	
CTU involvement				
Yes	18/26 (69.2)	0.682	10/26 (38.5)	0.881
No	14/22 (63.6)		8/22 (36.4)	
Missing	5		5	
Trial Management				
Dedicated Trial manager	29/39 (74.4)	0.019	16/39 (41.0)	0.294
No Dedicated trial manager	3/9 (33.3)		2/9 (22.2)	
Missing	5		5	
Additional Trial Demand				
Routine data collection for PO				
Yes	7/10 (70.0)	0.802	4/10 (40.0)	0.854
No	25/38 (65.8)		14/38 (36.8)	
Missing	5			
Additional test or procedure				
Yes	24/33 (72.7)	0.186	14/33 (42.4)	0.296
No	8/15 (53.3)		4/15 (26.7)	
Missing	5			
Additional hospital visit or ext. hospital stay				
Yes	11/19 (57.9)	0.297	4/19 (21.1)	0.057
No	21/29 (72.4)		14/29 (48.3)	
Missing	5			
Additional travel distance/time and/or associated costs				
Yes	10/15 (66.7)	1.00	6/15 (40)	0.809
No	22/33 (66.7)		12/33 (36.4)	
Missing	5			
Extra days off work/school and/or change in lifestyle of the family				
Yes	8/12 (66.7)	1.00	3/12 (25)	0.302
No	24/36 (66.7)		15/36 (41.7)	
Missing	5			
Extra paperwork for child/young adult/family				
Yes	14/19 (73.7)	0.404	10/19 (52.6)	0.08
No	18/29 (62.1)		8/29 (27.6)	
Missing	5			

*PO primary outcome, *SO secondary outcome, **9 studies were pilot/feasibility assessments

3.5 DISCUSSION

This study reviewed the recruitment performance of randomised controlled trials with children. The results show that 69% of the trials recruited to 100% target but only 35% recruited to target in the stipulated time frame or in a period not exceeding 10% of the planned recruitment period. The target was revised in 23% of the UK based trials and extension was requested in 49%.

Analyses to test association with a- priori factors, that were thought to affect recruitment, showed a significant association between trial management and successful recruitment. There was no significant association between recruitment success and being an IMP or non-IMP trial, trial of acute or chronic illness, CTU involvement, having a pilot or feasibility assessment prior to the study and additional trial demands on children, young people and/or families.

The strengths of the study were that it examined the recruitment performance of a comprehensive set of exclusively paediatric trials. The included trials were identified from the NIHR CRN portfolio implying these were well designed randomised controlled trials, eligible for research support from the NIHR Clinical Research Network. The cohort was a mix of publicly funded and commercial trials and included both international and UK studies. The trials covered a wide range of clinical areas and settings, different geographical centres and study teams and included small single centre to large multicentre trials. A previous review examined recruitment to a cohort of trials funded by the Medical Research Council (MRC) and National Health Service Health Technology Assessment (NHS HTA) programme between 1994 and 2002 (Campbell et al. 2007), but the number of paediatric trials in the review were limited to seven along with three

neonatal trials. To the best of our knowledge, this is the first study to review the recruitment performance of randomised controlled trials with children.

The study findings show that recruitment to randomised controlled trials with children is challenging. Under-recruitment and recruitment delays are a common problem, with trials needing revision of recruitment targets in a quarter and extensions in about half of the paediatric randomised controlled trials in the UK. In the previous review conducted by Campbell et al, 31% of trials recruited to 100% target and 54% recruited to 80% target (McDonald et al. 2006, Campbell et al. 2007). The recruitment target was revised in 34% of the trials and trial extension was requested in 54%. An update to this review assessed recruitment to a similar cohort of randomised controlled trials funded by the MRC and HTA between 2002 and 2008, which showed some improvement with 55% of the trials recruiting to target and 78% recruiting to 80% of target (Sully, Julious & Nicholl 2013). The recruitment target was revised in 19% and trial extension was requested in 47% of the trials. Our study shows that a higher proportion of randomised controlled trials recruited to 100% target, though a vast majority of trials had recruitment delays.

The reviews by Campbell et al and Sully et al looked at the percentage of studies that recruited to 100% target, irrespective of time frame. Additionally, they looked at studies that recruited to 80% of target but less than 100%. Our study defined recruitment success as recruiting to 100% target irrespective of time period but also adopted a stricter definition by defining recruitment success as recruiting to target in a period not exceeding 10% of the planned time period. This outcome is

likely to be more meaningful to trialists, clinicians and funding bodies, since it implies trial completion without a significant time delay.

The primary source of data was the NIHR CRN portfolio database, which is an actively monitored source of recruitment activity in the included trials. The recruitment data is uploaded on a monthly basis by the study teams through a secure online system. The data was also confirmed by contacting the Chief Investigators and study teams and verified from other sources such as Medicines for Children's Research Network (MCRN) coordinating centre to improve the accuracy and confirm the validity of collected data. The strength of the review was very little missing data. Our study defined recruitment success with reference to the originally planned recruitment target but a pragmatic approach was adopted. Each trial was considered on a case basis and the revised sample size accepted as target, if the reduction was due to reasons other than difficulties with recruitment such as a reduced drop-out rate.

The hypotheses of factors tested for association with recruitment success were generated a-priori to avoid being data driven. The initial sample size estimation of 150 randomised controlled trials on the NIHR CRN portfolio allowed for six factors to be tested. However, only 88 studies fulfilled the inclusion criteria for the review of which 61 recruited successfully, which was a reasonable number for six factors to be investigated based on an event per variable ratio of 10.

Our study showed that 'having a dedicated trial manager' was significantly associated with successful recruitment. Previous studies have reported the importance of good trial management to the successful conduct of a study (Menon et al. 2008, Farrell, Kenyon & Shakur 2010). In the review conducted by

Campbell et al, trials with a dedicated trial manager were more likely to recruit successfully, however the confidence intervals were wide and the result was not statistically significant at the 5% level (OR 3.8, CI 0.79-36.14, p 0.087). Other factors tested for association with recruitment success in this review were trial design, funding, dedicated trial management, multidisciplinary input, consumer involvement, pilot phase, nature of trial (drug vs. non drug, cancer trials) and intervention being available only in the trial. They found marginally significant association between recruitment success and being funded by MRC, being a cancer trial and not having paid local trial coordinators. However, the authors discuss that analyses performed to look at association between these factors and recruitment success were of limited value because of the choice of outcome and exposure variables and because of imprecision around estimates of association (McDonald et al. 2006, Campbell et al. 2007). There was some evidence that factors such as intervention being available only in the trial, having a dedicated trial manager and being a cancer or a drug trial may be associated with successful recruitment but the results were inconsistent and the authors report insufficient power to undertake a multivariable analysis.

Sully et al (2013) found that MRC funded trials appeared to recruit better than HTA funded trials but the results were not statistically significant. The clinical area of the trial appeared to affect recruitment success but the authors reported that the numbers were too small for a meaningful statistical analysis. CTU involvement was reported to be associated with improved recruitment to trials.

Our study found no statistically significant association between recruitment success and having a pilot/feasibility assessment and CTU support though trials

with these factors were more likely to recruit successfully. A potential explanation may be the confounding effect of trial complexity. Simple trials may be less likely to have a pilot/feasibility assessment or CTU involvement than more complex and difficult to recruit trials. Another possible explanation is that the services provided by a CTU other than a dedicated trial manager, may be less likely to affect trial recruitment.

The numbers were too small to draw conclusions with regards to the effect of additional trial demands on recruitment success but some interesting observations were made which can be investigated in future studies. Trials were more likely to recruit well if routine data collection was carried out or if a trial offered an additional test or procedure and less well if an additional or prolonged clinic visit or extended hospital stay was involved. Travel distance or time and associated costs and extra days off work or school for the family did not have any effect on recruitment success for non-commercial studies in the UK.

This review has some limitations. It tested some important factors for association with recruitment success but could not test factors that may affect parental consent. The study teams' perspective of additional trial demands on the family were tested for association with recruitment success but this is indirect evidence and the numbers were too small to derive any meaningful conclusion. It was difficult to measure the effect of patient and public involvement and as such this factor could not be tested.

Another limitation of the study was the presence of discrepancies in data obtained from the NIHR CRN portfolio and corresponding data obtained from the Chief Investigators/study teams. A huge amount of time and effort was invested in

collecting information from various sources, to be able to resolve these discrepancies. It was originally intended to calculate the recruitment rate to analyse achieved to anticipated recruitment, but the quality of the data did not permit this analysis. Global recruitment data had to be used to analyse the recruitment success of international studies as the discrepancies in data could not be resolved for these studies. The recruitment success of international studies could only be analysed for the primary outcome; data for calculation of secondary outcome was not reliably available. For the UK based studies, difficulties arising due to data discrepancies were overcome by obtaining information from various other sources and treating each trial on a separate case basis but adopting a uniform set of rules to resolve these discrepancies.

This review presents the collective picture of recruitment to paediatric trials. Recruitment to a clinical trial is affected by various intrinsic and extrinsic factors, relating to the study itself, clinical teams, patients, trial planning and conduct and the effect of media, publicity or external policies, to name a few. To understand the various factors that operate within a trial and their effect on recruitment, we planned to conduct a survey with the clinical teams of a multicentre randomised controlled trial with children, the MAGNETIC trial, to elicit their views on facilitators and barriers to recruitment to the trial. An evidence based recruitment survey tool was developed to capture the recruitment experience of clinical teams recruiting to a clinical trial.

Chapter 4

DEVELOPING A SURVEY OF BARRIERS AND FACILITATORS TO RECRUITMENT IN RANDOMISED CONTROLLED TRIALS

4.1 BACKGROUND

Recruitment to randomised controlled trials is known to be challenging. Prolonged or inefficient recruitment can have several adverse consequences (Gul, Ali 2010). Failure to achieve the target sample size can lead to a reduction in the statistical power of a study. An underpowered study may report clinically important effects to be statistically non-significant and result in delay or non-implementation of a clinically effective intervention and delay in identification of non-effective interventions. Prolonged recruitment results in increased time or cost extensions and may result in premature termination of trials. It is ethically unacceptable to conduct studies that terminate prematurely or fail to reach adequate statistical power (Treweek et al. 2013). It is important to understand and identify the predictors of good or poor accrual to a clinical trial so that appropriate strategies can be put in place to overcome these problems and facilitate successful trial completion.

Recruitment experience in existing studies

Several studies have examined recruitment experience from a number of perspectives. There are reports by trialists describing their recruitment experience, methods and strategies applied to increase recruitment (Baines 1984, Vollmer, Hertert & Allison 1992b, Strunk et al. 1999, Bailey et al. 2004, Heinrichs et al.

2005, Galbreath et al. 2008, Finne et al. 2009, Wardle et al. 2010). There are reports on recruitment and participation of under-represented populations such as minorities (Baquet et al. 2006, Nicholson et al. 2011) and adolescents and young adults in cancer trials (Fern, Whelan 2010). Studies have tried to assess parents' or families' reasons for participation or non-participation in trials (Peden et al. 2000, Mihrshashi et al. 2002, Wynn et al. 2010) and there are several reports of surveys and interviews with parents or patients investigating the same (Weintraub et al. 1980, Eiser et al. 2005, Cain, McGuinness 2005, Sharp et al. 2006, Dolan et al. 2008, Smyth et al. 2009, Driscoll et al. 2011, Nabulsi, Khalil & Makhoul 2011).

Surveys and interviews with clinical teams have investigated reasons for considering patients unsuitable for a trial (Hunt, Shepherd & Andrews 2001), reasons for not entering eligible patients (Taylor, Margolese & Soskolne 1984) and have explored difficulties with recruitment to the trial (Fairhurst, Dowrick 1996, Brooker et al. 1999). Caldwell et al (2002) conducted focus group discussions with sixteen paediatricians and five trainees from a paediatric teaching hospital to evaluate paediatrician's attitudes towards participation of children in randomised controlled trials and identify potential barriers to participation.

A number of studies have explored barriers to trial participation from patients and clinicians perspectives. Systematic reviews of studies (Ellis 2000, Cox, McGarry 2003, Tournoux et al. 2006) reporting barriers to participation in cancer trials have identified various patient and clinician related barriers. Fayter et al (2007) conducted a systematic review to investigate the barriers, modifiers and benefits of participation in randomised controlled trials of cancer therapies as perceived by

health care providers or patients and identified system-related or organisational barriers, trial design related and health care provider barriers. Twenty five included studies explored barriers to participation from the health care perspective with eight investigating recruitment to specific trials and seventeen studies investigating attitudes to trials in general. However, the authors concluded that the studies were of poor methodological quality and identified threats to internal validity in terms of potential for selection bias, non- justification of sample size, lack of reliability and validity of research instrument and problems of data collection. None of the included surveys in this systematic review provided a comprehensive list of facilitators and barriers to recruitment (Fayter, McDaid & Eastwood 2007).

Cook et al (2008) conducted a survey to explore the experiences, beliefs and practices of Critical Care Trials Groups regarding the effectiveness, feasibility and ethics of strategies to enhance enrolment and views on co-enrolment of critically ill children and adults into one or more clinical studies. Fernandez et al (2001) conducted a trial specific survey to explore the physicians' and parents' barriers to enrolment in the Children's Oncology Group's study of very low risk Wilm's tumour. Spaar et al (2009) conducted a postal survey among recruiting physicians in a multi-centre trial of respiratory rehabilitation in patients with chronic obstructive pulmonary disease to identify and weigh barriers to recruitment to the trial. The survey questionnaire comprised of barriers identified in literature which were applicable to the trial and concerns raised by recruiting physicians during the recruitment process.

Studies (Taylor, Margolese & Soskolne 1984, Fairhurst, Dowrick 1996, Brooker et al. 1999, Hunt, Shepherd & Andrews 2001, Fernandez et al. 2011) have examined barriers to recruitment in the context of a specific trial or a specific population and the survey questionnaires have been developed as trial or speciality specific (Cook et al. 2008). Spaar et al (2009) investigated some general barriers to recruitment as well but not comprehensively and recruitment facilitators were not identified.

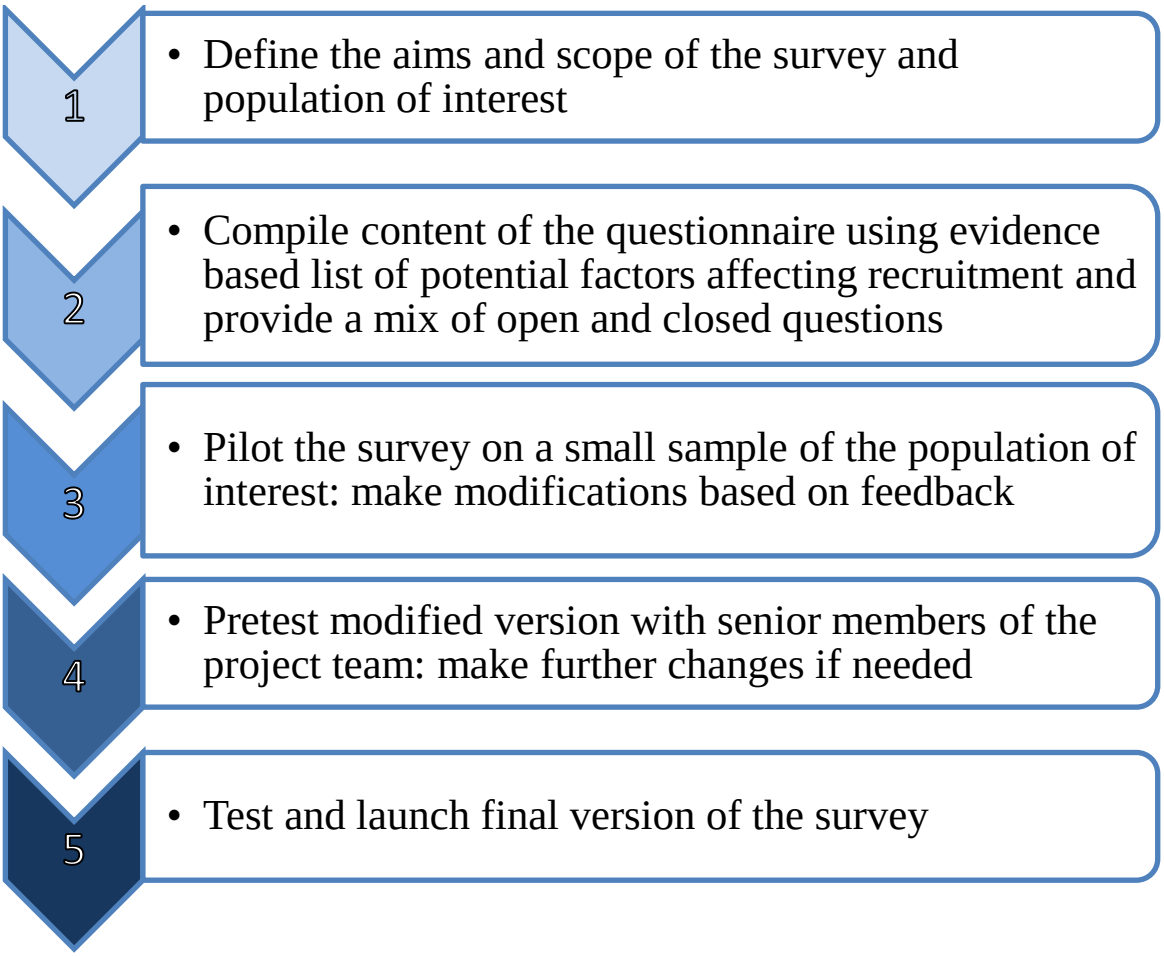
We developed a survey instrument which can be used to investigate the experience of clinical teams with regards to both facilitators and barriers to recruitment to a single/multicentre clinical trial in any clinical setting or speciality. The survey questionnaire is evidence based and has the potential to explore the generic factors affecting recruitment to a clinical trial with the scope of adding trial/speciality specific questions, thus providing a reliable tool and systematic approach to the recognition and management of recruitment problems. To the best of our knowledge, there is no such existing recruitment survey tool and we describe here the method of developing this survey questionnaire.

4.2 METHODS

4.2.1 Survey Design

The survey has been designed as an online questionnaire to be completed by study teams involved with recruitment to a trial. The process of developing the questionnaire is illustrated in Figure 2.

Figure 2: Process of developing the questionnaire



The survey is divided into four main sections to collect information about the site and study role of the responders, the perceived facilitators and barriers to recruitment, strategies applied to overcome the problems and suggestions for changes in organisation of future trials.

Free text space is provided for participants to enter information on their site/centre of recruitment, their role in the study and their duration and period of involvement if they were not involved for the whole trial recruitment period. It is possible to add questions for collecting information on if the centre was ever open to recruitment, the number of eligible patients for recruitment, numbers expected to be randomised and trust policy on recruitment to the study. Skip logic can be applied to direct questions selectively to responders depending on their response to past questions or skip questions if it does not apply to them.

The second section provides the survey participants with preformed lists of potential factors which could act as facilitators or barriers to recruitment, to be rated from -3 to +3, depending on whether the factor was perceived to be a strong (-3), intermediate (-2) or weak barrier (-1), 0 if thought to be not applicable and weak (+1), intermediate (+2), or strong facilitator (+3). Each factor could be assigned only one score. This question was designed in this format to enable us to deduce the most commonly identified strong barriers and facilitators and also calculate average scores for each factor.

The last section had open ended questions to gain information on the interventions applied and collate reflective experiences and suggestions of the study team to improve recruitment with space for additional comments. A copy of the survey questionnaire is presented in Appendix 17.

4.2.2 Writing the questionnaire

A list of potential facilitators and barriers affecting recruitment to randomised controlled trials was made from a review of existing literature on the subject. A literature search on Medline using the search terms ‘recruitment’, ‘enrolment’ combined with the AND connector to search terms for ‘clinical trials’ and ‘randomised controlled trials’ identified the major reviews on the subject that were used to develop the list of factors

The reviews used to design the survey questionnaire are briefly described below. The process of selecting and classifying the factors for inclusion in the survey questionnaire is illustrated in Table 13.

1. Prescott et al

The HTA report, ‘Factors that limit the quality, number and progress of randomised controlled trials’ by Prescott et al (Prescott et al. 1999) reported patient and clinician barriers to participation in randomised controlled trials. They conducted a systematic review of studies that reported problems related to recruitment of clinicians and patients to clinical trials and identified the important barriers.

2. Campbell et al

‘Recruitment to randomised trials: strategies for trial enrolment and participation study: The STEPS study’ aimed to identify the factors associated with good and poor recruitment to multicentre trials (Campbell et al. 2007). They conducted an epidemiological review (The STEPS study Part A) of a cohort of trials funded by the MRC (Medical Research Council) and the NHS HTA (National Health

Service Health Technology Assessment) programme between January 1994 and December 2002. They tested hypotheses of factors for association with recruitment success in the cohort of multicentre randomised controlled trials included in the review, described patterns of recruitment and reported trialists' perceptions of factors associated with good or poor recruitment. The study also reported the reasons for delay in recruitment and early and late participant recruitment problems in the included cohort of trials based on the trialists' reports submitted to the funding bodies. The STEPS study (Part B) reported case studies of trials that recruited successfully and had particularly interesting lessons for recruitment. This part of the study was aimed to gain role specific and location specific insights to the four included trials by interviewing 45 individuals in total across the four trials with different internal perspectives. They identified four key stages of a trial that may affect recruitment: *foundation work* involving engagement of collaborators, establishing scientific rigour, funding and financial considerations, *recruitment processes*, *delivery of care* and *delivery of research* and reported common factors in the success of these trials based on analysis of themes identified in these key stages and from the responses of the interviewees.

3. Toerien et al

Toerien et al reviewed the recruitment and retention rates in randomised controlled trials published in six major journals between July and December 2004 and investigated their association with trial characteristics such as study size, number of arms, single/multicentre, treatment focus (drug/surgery/allied/others), active/placebo control, time to assessment and type of funding (Toerien et al. 2009).

4. Caldwell et al

The systematic review of strategies for increasing recruitment to randomised controlled trials by Caldwell et al (2010) looked at the effect of recruitment interventions such as novel trial designs, recruiter differences, incentives and different methods of providing trial information on recruitment success in randomised clinical trials.

5. Treweek et al

The Cochrane systematic review on strategies to improve recruitment to randomised controlled trials (Treweek et al. 2010) identified 45 randomised and quasi-randomised controlled trials of interventions directed at potential participants or clinicians, which aimed to improve recruitment of participants to clinical trials. These interventions were divided in six categories: design change, modification to the consent form or process, modification to the approach made to potential participants, financial incentives for participants, modification of training given to recruiters and greater contact between trial co-ordinator and trial sites.

From the facilitators and barriers reported in the above studies (Prescott et al. 1999, Campbell et al. 2007) and the potential factors and interventions tested for association with recruitment success (Campbell et al. 2007, Toerien et al. 2009, Treweek et al. 2010, Caldwell et al. 2010), a list of potential factors affecting recruitment was generated by classifying the facilitators and barriers into various categories. This process is illustrated in Table 13. The factors that were generic and expected to operate commonly at all sites were classified as *trial level factors*. These included factors such as funding for the trial, trial design, choice of patient

inclusion criteria, type of intervention, previous pilot/feasibility assessment, perception of clinical equipoise, publicity about the trial, trial management etc. The factors which could operate differentially between sites were classified as *site level factors* and included factors such as time to open up site, recruitment target, local clinical arrangements, number and availability of trained staff, competing research projects and local research culture to list a few. We excluded factors for which objective information is available such as delays in ethical clearance, R&D delays, and problems with supply of investigational drug/placebo etc. The various facilitators and barriers relating to patients' and clinicians' participation in clinical trials, as described in the above studies were listed under *patient related and clinical team related factors*. The factors related to providing information to patients and seeking consent such as amount and complexity of trial information, clarity in presentation of trial information, time and setting of consent seeking and role and seniority of person seeking consent were categorised separately as *information and consent related factors*. Lastly, the study team factors such as motivation and research experience of study team, communication and coordination between research teams were presented. Each category formed a separate question in the survey questionnaire to help the participants think through the issues arising during recruitment to the trial.

Table 12: Deriving the factors affecting recruitment from facilitators and barriers described in literature

1. Prescott et al		
Barriers to participation in clinical trials: patient and clinician barriers		
Barriers	Classification	Factor derived
Patient barriers		
Additional demands of the RCT on the patient additional procedures, additional appointments, time pressures, venepuncture, inpatient hospital stays, discomfort from medical procedures, length of study, worry about experimentation, uncomfortable procedures, travel and travel costs, extra costs	Patient level factors	Additional trial investigations Additional travel and extra costs Duration of trial and follow up
Patient preference for a particular treatment wish not to change medication, not to take placebo, not to take experimental medication, not to take any medication, patient request for a specific intervention, strong patient preference for one treatment option *Aversion to treatment choice by random allocation*	Patient level factors	Patients'/parents' preference for a particular treatment Patients'/parents' attitude towards their taking experimental medicine or placebo Treatment choice by random allocation
Worry about uncertainty efficacy of treatment on offer is unproven, distrust of hospital or medicine, fear of unknown	Patient level factors	Patients'/parents' concerns about side effects of new drug
Concerns about information and consent amount of information provided to research participants, wording of information, complexity of information provided, different forms of information presentation: written /verbal/video,	Information and consent related factors	Amount and complexity of trial information provided Clarity in presentation of trial information

limited reading skills and English not being the primary language, clinicians experience, difficulty in giving information, worry about level of information required and that information may be frightening, consent procedure barrier to recruitment	Patient level factors Clinical team factors	Experience and training of clinical team seeking consent Social and emotional dynamics of trial discussion Consent rate Language or cultural barrier Difficulty in approaching patents for consent
Clinician barriers		
Time constraints time pressures from usual clinical practice, time demands of recruitment and follow up	Clinical team factors	Clinical workload
Staffing and training lack of trained staff, no additional support, lack of research experience in clinicians, lack of available support staff	Clinical team factors	Research experience of clinical team Availability of designated research team Availability of research staff out of hours Presence of designated research nurse/practitioner
Rewards and recognition economic incentives	Excluded	Information available from the Chief Investigator
Impact on doctor patient relationship fear of adverse effect on doctor-patient relationship, perceived conflict in their role as clinicians and researchers *Concern for patients*	Clinical team factors	Clinician attitude to involving patients in research

concern about treatment toxicity, side effects, burden of trial for patients including travel distance and costs, reluctance to recruit severely ill patients		
Problems in complying with the protocol	Clinical team factor Trial level factor	Clinician preference for a particular treatment Study protocol compared to clinical practice
2. Campbell et al		
Hypothesis of factors tested for association with recruitment success		
Trials with complex trial design do not recruit as well as simple trials	Trial level factor	Trial design
Less well funded trials do not recruit well	Trial level factor	Funding
Trials without dedicated trial management expertise do not recruit as well as those with trial management expertise	Trial level factor	Trial management
Trial with multidisciplinary input recruit better than those that do not have this input	Excluded	Information available from the Chief Investigator
Trials with consumer involvement recruit better than those that do not	Excluded	Information available from the Chief Investigator
Trials that have a successful pilot phase recruit better than those that do not have a pilot phase	Trial level factor	Previous feasibility assessment Previous pilot trial
Trials that have dedicated paid local coordinators recruit better than those that do not	Trial level factor	Trial management
Cancer trials recruit better than non-cancer trials	Trial level factor	Being a drug/cancer trial
Drug trials recruit better than non-drug trials	Trial level factor	Being a drug/cancer trial
Trials funded through a response mode	Trial level	Funding

funding have different recruitment rates to those funded through a commissioned process	factor	
Reasons for delays in recruitment to the included cohort of trials		
problems with central staff, local research staff, internal problems e.g. staff	Site level factor Clinical team factor	Number of trained staff Motivation of clinical team
local clinical arrangements, merging / reorganisation of trusts, major relocation of services, department policies	Site level factor	Local clinical arrangements
funding issues	Trial level factor	Funding
delays in ethical clearance, MREC, LREC R&D delays, time delay since grant application	Excluded	Information available from the Chief Investigator
delays in supply of drug/placebo	Excluded	Information available from the Chief Investigator
adverse publicity about medical research, external problem e.g. publicity	Trial level factor	Publicity by the trial team External publicity
setting up GP practices took longer than anticipated	Site level factor	Time to open up site
simultaneous other local research projects, competing research, conflict with other trials	Site level factor	Competing local research projects
delays due to changes in data legislation, changes in technology	Excluded	Information available from the Chief Investigator
fewer eligible than expected, smaller percentage agreeing to participate, recruitment targets too ambitious	Trial level factor Site level factor	Lack of pilot/feasibility assessment Recruitment target
absence of perceived clinical equipoise	Trial level	Clinical equipoise

	factor	
issues with procedures/interventions trial process too demanding	Patient level factor	Additional trial investigations
complexity of trial design, trial methodology considered too complex	Trial level factor	Trial design
conflicting workload pressures, long waiting lists, additional theatre time required	Clinical team factor	Clinical workload
language/written English difficulties	Patient level factor	Language or cultural barrier
treatment preferences	Patient level factor Clinical team factor	Patients'/parents' preference for a particular treatment Clinician preference for particular treatment
research not considered as priority	Clinical team factor	Perceived importance of research generally in clinical practice Perceived importance of the particular research question
no local access to intervention	Patient level factor	Intervention available only in the trial
Case studies of trials: common factors in the successes of part B trials		
Facilitator	*Classification*	*Factor derived*
Important/interesting research question, topic important, urgent need for research, important question, timely and managed to roll several questions into one study	Clinical team factor	Perceived importance of the particular research question
Good design/good protocol, pragmatic study	Trial level factor	Trial design Study protocol compared to clinical practice
Clinicians keen to recruit to trial	Clinical team factor	Motivation of clinical team Clinician attitude to

		involving patients in research
Drugs already tested, so easy to explain to patients	Patient level factor	Familiarity with experimental treatment
Didn't demand extra effort from patients, Impact on practice running and costs minimised, minimising work for health professionals	Patient level factor	Additional trial demands
No competing trials for those centres/patients	Site level factor	Competing local research projects
Drugs not available outside the trial	Patient level factor	Intervention available only in the trial
Excellent trial management, trial units helpful, caring, annual meetings for all concerned, role of trial steering group Good planning and organisation by CTSU, CTSU responsive, efficient, central organisation of many aspects of research	Trial level factor	Trial management
Good communication between trial team and clinicians, flexibility of trial teams	Study team factor	Communication and coordination between study team members at site
Good public relations/feedback/updates	Trial level factor	Trial publicity
Good funding, NHS funding	Trial level factor	Funding
Trial run by good team/infrastructure, PI well respected, PIs worked hard to keep collaborators on board, trial team communicative, responsive and alert to problems. Communication within team, between team and collaborating clinicians Good trial team, good research assistants	Study team factors	Motivation of the study team at site Research experience of PI and study team members at site Communication and coordination between study team members at site

Team worked hard at how to explain the study to patients	Clinical team factor	Communication and coordination between study team at site and CTU Research experience of clinical team Communication skills of clinical team
Role of research nurse	Clinical team factor	Presence of designated research nurse/practitioner
Study included everybody	Trial level factor	Patient inclusion criteria
3. Toerien et al		
Study design, number of arms, control: active/placebo	Trial level factor	Trial design
Single/multi-centre	Excluded	Information will be present
Intervention: drug/surgery/allied/others	Trial level factor	Being a drug/cancer/surgical/----- trial
Funding source	Trial level factor	Funding
4. Caldwell et al		
Recruitment strategies		
Novel trial designs	Trial level factor	Trial design
Recruiter differences	Information and consent related factors	Experience and training of doctors clinical team seeking consent Senior doctors and nurses seeking consent
Financial incentives for patients/participants	Excluded	Monetary incentives not acceptable for clinical research in UK

Methods of providing information	Information and consent related factors Patient level factor	Amount and complexity of information provided Clarity in presentation of trial information Consent rate
5. Treweek et al		
Recruitment strategies		
Design changes	Trial level factor	Trial design
Modification to the consent form or process	Patient level factor	Consent rate
Modification to the approach made to potential participants	Information and consent related factors	Amount and complexity of information provided Clarity in presentation of trial information Senior doctors and nurses seeking consent
Financial incentives for patients/participants	Excluded	Monetary incentives not acceptable for clinical research in UK
Modification to the training given to recruiters	Information and consent related factors	Experience and training of clinical team seeking consent
Greater contact between trial co-ordinator and trial sites	Trial level factor	Trial management

This section of the survey could be designed to elicit only barriers, only facilitators or both barriers and facilitators to recruitment. In order to decrease the length of the survey and capture information on both facilitators and barriers in a common question, the factors were reworded such that they could apply both as a facilitator or barrier depending on whether they boosted or hindered recruitment respectively. The questions in this section were designed to obtain graded responses from -3 to +3, as described earlier. Open type questions were provided to obtain information on the various strategies applied to overcome the problems and for participants to express their reflective experiences and views on how trials could be organised differently in the future to improve recruitment.

4.2.3 Pretesting/Piloting the questionnaire

The paper version of the questionnaire was sent for piloting to a small sample of 5 people. 3/5 people (60%) responded. The initial version had separate lists of facilitators and barriers and participants were asked to identify the top 5 in each list. Two out of the three respondents found the questionnaire lengthy, difficult to complete and it took them 35-40 minutes to do so. Some questions were thought to be ambiguous and there was a suggestion for use of computers to enhance the presentation and make it easier to complete.

After the pilot, the questionnaire was modified. The length of the questionnaire was reduced by combining the facilitators and barriers into a single list of factors that could be graded as either in the same question. Efforts were made to provide an evidence-based list of factors affecting recruitment while taking measures to keep the length of the survey and time of completion within reasonable limits. Factors, for which objective information was thought to be available from other

sources, such as delays in ethical or R&D approval or problems with supply of investigational drug/placebo were excluded from the questionnaire. However, free text space for additional comments was provided at the end for responders to note any issues not covered in the survey.

The factors were reworded so that they were simpler and clearer. An online version was created by using a survey software (www.surveygizmo.com). The questions were arranged such that they had a logical flow. Each category of factors was arranged as small separate sections on a webpage for better presentation and ease of completion. The participants could easily navigate forwards and backwards to re-visit a section if they needed to and the completion time was restricted to 10-15 minutes.

The survey instrument was used to investigate the recruitment experience of clinical teams in a large multicentre randomised controlled trial with children in the UK (the MAGNETIC trial), as described in Chapter 5.

5.3 DISCUSSION

A survey is a systematic method of collecting data from a population of interest, usually through the use of a structured and standardized questionnaire (Conducting Survey Research 1999). The methods of conducting survey research can be interviews, either face to face or telephonic, or using postal or electronic questionnaires. The advantages of a participant completed questionnaire over an interview are that it is quicker and cheaper, avoids interviewer bias and allows respondents to record their responses privately even to sensitive issues. The disadvantages are that questions may be misunderstood or not fully answered by

the respondent and the need to rely more on closed questions to ensure consistency in the range of answers for a question and for ease of analysis (Bruce, Pope & Stanistreet 2008). E-surveys offer a number of advantages over paper or telephone survey techniques in terms of lesser time and cost requirements, better accuracy in terms of lesser data transcription errors, faster creation and delivery, enhanced presentation and higher response rates. The potential disadvantages include response bias resulting from unequal access to internet, issues of authenticity, data security and confidentiality, and respondent non-response or procrastination (Anderson, Kanuka 2003).

For these reasons, the recruitment survey questionnaire was developed as an online tool. Care was taken to avoid errors due to respondent misinterpretation of questions by phrasing the questions in a simple and clear manner. A mix of open and closed questions was provided to obtain accurate responses but also provide respondents the freedom to express their views. Efforts were made to make the survey user friendly by arranging the questions in a logical order and restricting the length of the survey. However, as for any other survey instrument the generation of useful results depends on a good response rate from a representative sample of the population of interest and obtaining true and accurate responses from participants.

Recruitment to a clinical trial and its conduct is shaped by various internal and external forces including the shifting dynamics at sites because of changes in jobs/roles of staff including periodic turnover of trainee doctors every few months and change in policies at the hospital or trust level. Understanding the working of individual trials and of trial teams at various sites in a multicentre trial, with their

unique challenges, as well as the responses of the research teams to these challenges can provide important information that can be used to inform the design and conduct of future trials (Campbell et al. 2007).

This survey questionnaire could be a very useful tool to investigate the recruitment experience of clinical teams and identify facilitators and barriers to recruitment to a single or multi-centre clinical trial in any clinical setting or speciality involving adults or children. It provides a common list of questions to participants at multiple sites and can be used to elicit the facilitators and barriers to trial participation in general but can be adapted and modified by adding trial specific questions and highlighting trial/speciality specific recruitment issues. It is designed to gather data from people with a range of responsibilities related to recruitment to the trial. It can be aimed at staff directly involved with recruitment but can also be extended to other staff that facilitate recruitment or are involved indirectly to gain an insight into their perspective on issues around recruitment to the trial. The survey can be easily sent to a large number of participants at the same time. It can be used to gauge role and site specific perceptions of the research team and can provide a detailed understanding of the various factors affecting recruitment in addition to information provided by other monitoring tools such as screening logs.

This survey tool was designed to be used at the end of the recruitment phase of a study to identify useful lessons for future research and other trialists. It could be used however, with some modification, in the pre-trial phase to identify potential problems or in the early and middle recruitment phases when observed participation rate is lower than expected. During a trial, the study team will often

contact under-recruiting sites to obtain information about problems encountered or higher than average recruiting sites to identify facilitators. This tool would provide a more systematic approach to the collection and consideration of such information, ensuring that all evidence-based barriers and facilitators are reviewed by the site in their response, so that appropriate strategies can be implemented to overcome the problems identified. If the survey is to be undertaken during the recruitment phase to identify modifiable aspects of the process, factors such as the time taken to open the site and whether there was a previous feasibility or pilot study would not be relevant.

Since recruitment performance is usually variable at different sites, it can be used to investigate the various site specific issues. This will not only provide a detailed understanding of the internal milieu of the trial but also provides the opportunity for comparison of responses between successful and non-successful sites. Identification of facilitators or barriers and strategies applied at sites with successful recruitment in comparison to less successful sites may highlight some modifiable differences, which can form the basis of interventions and strategies to boost recruitment to an ongoing clinical trial or provide useful lessons for designing and conducting future trials.

The survey questionnaire has some potential limitations. Being a subjective tool, it is prone to responder misinterpretation and the authors encourage trialists to pilot the questionnaire with a sample of their trial team prior to use to ensure consistent understanding of the listed factors. Exclusion of factors such as monetary incentives may potentially limit the applicability of the survey in settings where financial incentives are accepted practice.

Although it has been designed to provide an evidence based list of generic factors that affect recruitment to clinical trials, the authors would again encourage trialists to think about other anticipated or observed trial specific issues and modify and adapt the questionnaire before use taking into consideration the type of trial and the stage of recruitment. The length of the survey can be reduced further by excluding factors that are thought to be irrelevant to a particular trial.

This recruitment survey tool was used to elicit barriers and facilitators to recruitment of children to the MAGNETIC trial, as described in the next Chapter.

Chapter 5

A SURVEY OF FACILITATORS AND BARRIERS TO RECRUITMENT TO THE MAGNETIC TRIAL

5.1 BACKGROUND

Conducting clinical trials with children presents a unique set of challenges due to the vulnerability of the population. There are ethical considerations including the need to protect them from harm, and issues around obtaining informed consent, which is usually given by parents. There are other methodological issues which can make recruitment to paediatric trials challenging. The burden of disease in children due to chronic illness is relatively small; certain conditions may be uncommon reducing the pool of eligible population for a trial and the diagnostic criteria may be less precise and difficult to apply (Smyth, Weindling 1999, Smyth 2001).

Recruitment to a randomised controlled trial can be affected by an array of internal and external factors, which are important determinants of trial success or failure. Understanding the various factors that operate in a trial setting and at various sites in a multicentre clinical trial, along with the response of the clinical teams to overcome the challenges, can provide important information that can be used in the planning, design and conduct of future clinical trials (Campbell et al. 2007).

Several studies have investigated clinical teams' perspectives on barriers to patient recruitment (Spaar et al. 2009b, Fernandez et al. 2011) and their experiences, beliefs and attitudes (Caldwell, Butow & Craig 2002, Cook et al. 2008) to patient participation in trials, as discussed in Chapter 4. Systematic reviews (Ellis 2000, Cox, McGarry 2003, Mills et al. 2006, Tournoux et al. 2006) of studies reporting barriers to participation in cancer trials reported various physician and patient related factors along with system or organisational barriers and other factors relating to protocol, stage of disease, associated co-morbidities, age, gender, ethnicity, and sociocultural factors etc. However, none of the included surveys in these reviews provided a comprehensive list of barriers and facilitators. An assessment of study quality by Fayter et al (2007) showed the studies to be methodologically poor and highlighted several threats to internal and external validity of the included studies in terms of vulnerability to selection bias; lack of a reliable and validated survey instrument, and poor reporting of methods of recruitment, data collection and data analysis. We conducted a survey of facilitators and barriers to recruitment with the clinical teams of a multicentre randomised controlled trial with children: the MAGNETIC trial (Powell et al. 2013) using the recruitment survey tool, described previously.

MAGNETIC trial

The MAGNETIC trial was a randomised, multicentre, double blind, placebo controlled study evaluating the role of nebulised magnesium in severe acute asthma in children, unresponsive to standard inhaled treatment. Two to sixteen year old children presenting to the emergency department or children's assessment unit with acute severe asthma were given conventional treatment on

presentation. They were reassessed after 20 minutes of conventional treatment and children who met the criteria for severe asthma after 20 minutes of standard inhaled therapy were enrolled into the study. Written informed consent was obtained from the parents or guardians in the 20 minute period when the child was receiving initial treatment. The MAGNETIC trial recruited from 30 sites across the UK. There were three other sites which had opened, but could not recruit any patients and a further four, where efforts were made to set up the trial but they did not open to recruitment (Powell et al. 2013). The list of sites is presented in Appendix 18.

The MAGNETIC trial was chosen for surveying the clinical teams and investigating the facilitators and barriers to recruitment for a number of reasons. It was a large multicentre RCT that successfully recruited over 500 children from 30 sites across the UK. The recruitment performance at sites was variable and therefore it was anticipated that surveying the clinical teams at all sites would provide a rich source of data on a wide range of facilitators and barriers to recruitment. Responses from the more successful sites could provide useful learning lessons in terms of facilitators and strategies adopted by clinical teams to overcome the identified barriers. On the other hand, responses from less successful sites could provide useful insight into barriers to recruitment and hurdles that were difficult or impossible to overcome. Additional logistical considerations that favoured the choice of MAGNETIC was that the trial had recently closed to recruitment and the timing of the survey was ideal to explore the recruitment experience of clinical teams.

5.2 AIMS

The aims of this survey were:

1. To establish the perception of clinical teams with regards to facilitators and barriers to recruitment to the trial.
2. To elicit information on recruitment strategies or interventions, that were applied at various sites to improve recruitment
3. To seek reflective comments from the study teams on how the trial could have been organised differently

5.3 METHODS

5.3.1 Survey tool

The survey was conducted using an online questionnaire adapted from the web based recruitment survey tool described in Chapter 4 (Kaur, Smyth & Williamson 2012). The questions were worded to apply specifically to the MAGNETIC trial. A copy of the survey questionnaire is presented in Appendix 19.

5.3.1.1 Writing the questionnaire

The *first section* was designed to collect information on responder characteristics such as the ID of the responder, study role, name of the hospital or site they were recruiting from and duration and period of involvement in the trial. Personal information such as name of individuals were not collected, but each potential responder was issued a unique identification number for data management purposes, which was sent to them in the email inviting them to participate. The *second section* was designed to elicit information on their perception with regards

to facilitators and barriers to recruitment to the trial. The responders were asked to score a preformed, evidence based list of potential factors (Table 14) affecting recruitment to a clinical trial. These factors were categorised in terms of operating at the level of trial, site, patient, clinical team, information and consent process and central study team. The responders were asked to grade each factor from -3 to +3 depending on whether the factor was perceived as a strong (-3), intermediate (-2), or weak (-1) barrier, or weak (+1), intermediate (+2) or strong (+3) facilitator and (0) if thought to be not applicable.

The *final section* was designed to collect information on interventions or strategies that were applied at sites, to overcome the barriers that were identified and the effectiveness of these interventions. The responders were then asked for their views on how the trial could have been organised differently to improve recruitment. The responders were invited to give additional comments, if any.

Table 13: Factors listed in the recruitment survey questionnaire

Trial level factors
Funding
Trial design
Patient Inclusion Criteria
MAGNETIC being a drug trial
Study protocol compared to clinical practice Clinical equipoise
Previous feasibility assessment
Previous pilot trial
Publicity by the trial team
External publicity
Trial management
Protocol amendments
Seasonal variation
Site level factors
Time to open up site
Recruitment target
Time to complete administrative work related to the trial
Number of trained staff
Local clinical arrangements
Choice of recruitment setting
GCP training
Data collection process
Competing local research projects
Local research culture
Patient related factors
Consent rate
Familiarity with experimental treatment
Parent's attitude towards their taking experimental medicine or placebo
Parent's preference for a particular treatment
Parent's concerns about side effects of new drug
Duration of trial and follow up
Treatment choice by random allocation
Additional trial investigations
Additional travel and extra costs

Intervention available only in the trial
Communication between research team and parents
Clinician influence
Language or cultural barriers
Clinical team related factors
Research experience of clinical team
Presence of designated research nurse or practitioner
Availability of designated research team
Availability of research staff out of hours
Shift patterns of work
Motivation of clinical team
Clinical workload
Perceived importance of research generally in clinical practice
Perceived importance of the particular research question
Communication skills of clinical team
Clinician preference for particular treatment
Clinician attitude to involving patients in research
Difficulty in approaching patients for consent
Information and consent related factors
Amount and complexity of trial information provided
Clarity in presentation of trial information
Social and emotional dynamics of trial discussion
Time and setting of consent seeking
Senior doctors and nurses seeking consent
Experience and training of clinical team seeking consent
Study team factors
Motivation of MAGNETIC study team at site
Communication and coordination between study team members at site
Communication and coordination between study team at site and CTU
Research experience of PI and study team members at site

5.3.1.2 Developing the online survey

The survey questionnaire was developed using the survey gizmo software (www.surveygizmo.com). Each question was designed using the appropriate question type. Textbox design was used for questions asking about the ID of responders and name of site they were recruiting from. Checkbox style was used for responders to select options such as period of involvement in the trial. The question on factors affecting recruitment was presented as a radio-button grid, so that responders could select a single option only and give each factor only one score. The open questions on recruitment interventions and reflective comments were designed using essay type questions to provide appropriate space and word limit for responders to express themselves freely. Anonymity was maintained and no personal information was collected.

The questions were arranged in a logical sequence. The section on responder characteristics was followed by section on choice of factors affecting recruitment to be followed by open questions on recruitment strategies and comments on organisation of the trial. A small number of questions were presented on a webpage. Each category of factors was presented on a separate webpage for better presentation and ease of completion. Skip logic was applied to direct questions to responders based on their response to the previous question, so that they may skip questions that were not relevant to them. The users could navigate forwards and backwards to revisit questions, if needed and the option to save progress and continue at a later time was available, using the web link that was sent to them.

5.3.1.3 Testing the survey

The survey questionnaire was tested with the senior members of the research team (PW, CP) prior to launch. They were requested to complete the test versions of the survey using a test web link. The display of questions and webpages was checked. It was ensured that the survey software was functioning adequately to ensure that the questions could be answered accurately and the respondents could 'save and return' and navigate through the survey as planned. The survey software was able to calculate the approximate time taken to complete the survey and this was crosschecked with the actual time taken at the testing stage. Data validation checks were conducted. Test surveys were completed by GK and the responses collected and reported in the survey exports were crosschecked with the actual responses entered to ensure data was collected and reported accurately by the survey software. The test links to the survey were emailed via the automated email system to ensure that the emails were delivered appropriately, in the correct format and that the respondents could be tracked by the survey software.

5.3.2 Ethical considerations

The University of Liverpool and National Research Ethics Service (NRES) was contacted to check if ethical clearance was required prior to conducting the survey. The University of Liverpool directed the query to NRES, as National Health Service (NHS) staff was involved in the survey. The project details were sent to the queries line at National Research Ethics Service (NRES), and they confirmed that that ethical approval was not needed for this project, as per the 'Defining Research' guidance issued by the NHS National Patient Safety Agency

(National Research Ethics Service). The correspondence with University of Liverpool and NRES is presented in Appendix 20.

5.3.3 Administration of the survey

5.3.3.1 Sites

The survey was intended to be conducted at all 37 sites as recruitment experience was envisaged to be different at the various sites. The Chief Investigator of the MAGNETIC trial wrote to Principal Investigators at all sites requesting their participation in the study. GK emailed the Principal Investigators subsequently, to seek permission to contact clinical staff at that site. The survey was emailed to clinical staff at sites, once permission was obtained from the PI, following which their contact details were requested from the NIHR Medicines for Children Research Network Clinical Trials Unit, who were responsible for managing the trial.

5.3.3.2 Contact Details

The names and email addresses of clinical staff involved with recruitment to the trial were requested from the NIHR Medicines for Children Research Network Clinical Trials Unit. Staff allocated to one or more of the following roles on the delegation log were identified to be contacted:

- A- screening of patients
- C- obtaining informed consent
- D- prescription of trial treatment
- E- Asthma severity score training

Roles A and C included staff directly involved in recruiting to the trial. Additional roles such as prescription of trial treatment and conducting asthma severity scoring training were selected to include clinical staff, who could provide valuable insight into the various patient and clinical team related factors and comment on training related issues if any. It was taken into consideration that the roles will overlap and individuals will have multiple roles; for example person delegated to perform 'D' will also be delegated to perform 'A' and/or 'B' but this approach was taken to minimise the chances of missing the relevant people involved in recruitment to the trial.

5.3.3.3 Invitation to participate in the study

An initial invitation describing the aims of the survey provided the link to the questionnaire. Voluntary participation was requested and potential responders were reassured that no personal information will be collected, no sites will be identified in any publication and confidentiality of data will be maintained. Each responder was issued a unique identification number for data management purposes. A copy of the invitation letter is presented in Appendix 21.

5.3.3.4 Reminders to non-responders

The non-responders were sent two subsequent reminders spaced four weeks apart. The initial invitation and the reminders were sent using the automated email system of the survey software. Additional email and telephonic reminders were sent to principal investigators and research nurses, who did not respond to the questionnaire despite the two reminders.

5.3.4 Data collection

5.3.4.1 Collecting survey responses

The responses to the questionnaire were collected online. The responders had the option to save their progress and continue at a later time. These responses were logged as ‘partial’ responses. A response was categorised as ‘complete’, once it was submitted.

5.3.4.2 Eligible population at site

The Health and Social Care Information Centre (HSCIC) was requested for information on the number of two to sixteen year old children with asthma or wheeze, presenting to the Accident and Emergency departments of the hospitals which were the recruiting sites for the MAGNETIC trial. This data was requested to ascertain an estimate of the size of the eligible population at sites. However, data on diagnosis and the number of A&E admissions at each hospital site were not available; this data could only be obtained at the corresponding NHS trust level. The total number of annual A&E admissions in the given age group was taken as a proxy indicator of the eligible population at each site, making the assumption that the relationship between overall population size and the number of eligible children presenting to A&E is the same across all sites. This data could be obtained only for the 25 English sites.

5.3.4.3 Calibrated site recruitment

Site recruitment was calibrated to account for the hospital population base, by dividing the number recruited at site by the number of 2-16 year old children presenting to Accident & Emergency department at the corresponding NHS trust,

during the period the site was open for recruitment. The MRC Clinical Trials Unit was requested for information on the duration of recruitment and number of patients randomised at each site. Proportionate eligible population for the duration of recruitment at each site was then calculated. The calculations are shown below:

1.Eligible population for the duration of recruitment at site (EP)

$$= \frac{\begin{matrix}Annual\ number\ of\ AE\ attendance \\ in\ the\ corresponding\ NHS\ trust\ (2010-2011)\end{matrix}}{365} \times \frac{number\ of\ days\ the\ site\ recruited\ for}{}$$

Number of days the site recruited for

$$= date\ of\ final\ randomisation\ at\ site - date\ of\ site\ initiation$$

2.Calibrated site recruitment (CR) = $\frac{Number\ randomised\ at\ site}{EP}$

5.3.5 Data Analysis

5.3.5.1 Facilitators and barriers to recruitment

Commonly identified facilitators and barriers were defined *a priori* as those that were identified as a facilitator or barrier by 50% of the responders or more. In addition to the overall responses, the PI and research nurse responses were analysed separately. One PI and one research nurse response per site was included in the analysis to ensure equal representation of sites.

5.3.5.2 Recruitment strategies

The free text responses were grouped into themes to identify the recruitment strategies that were applied to overcome the hurdles that were identified at various sites.

5.3.5.3 Comments on how the trial could have been organised differently to improve recruitment

The free text responses were grouped to identify the recurring themes on the subject.

5.3.5.4 Statistical analysis

The survey data was exported to an excel spread sheet and analysed using Microsoft Excel 2010. NVivo, qualitative data analysis software package (QSR international Pty Ltd. Version 10) was used to assist analysis of free text responses for identification of recruitment strategies and recurring themes on organisation of the trial to improve recruitment. The association between PI response and calibrated site recruitment was examined using Spearman's rank correlation and linear regression using SPSS 20 (IBM SPSS Statistics for Windows, Version 20, Armonk, NY).

5.4 RESULTS

5.4.1 Administration of the survey

A list of 656 potential contacts was obtained from the study delegation log of which contact details could be obtained for 491. This included Principal Investigators and research nurses, where available, at all 37 sites and other clinical staff at 30 of the 33 open sites; permission to contact other staff could not be obtained from the Principal Investigators at the remaining 3 sites.

The survey was conducted from August 2011 to February 2012. The link to the online survey was e-mailed to available contacts comprising of principal

investigators, research nurses and clinical staff involved with recruitment, such as medical practitioners, nurse practitioners and nursing staff.

5.4.2 Survey responses

5.4.2.1 Overall responses

A total of 206 responses were received- 169 complete and 37 partial responses. Of the 37 partial responses, 14 were duplicate responses, no data were recorded in 20 and less than 25% of the questions were answered in 3. These were excluded from analysis. The number and percentage of overall responses by role, duration and period of involvement is shown in Table 15.

Table 14: Number (%) of responses by role, duration and period of involvement

	n	%
Role (n=169)		
PIs	33	19.5
Medical Practitioners	71	42
Research Nurses	42	24.9
Others	23	13.6
Duration of involvement (n=169)		
Whole trial period	92	54.4
Part of trial period*	75	44.4
No response	2	1.2
***Period of involvement (n=75)**		
Set up/early recruitment period	14	18.7
Once trial established at site	54	72
Both	3	4
No response	4	5.3

**period of involvement for responders who were not involved for the whole trial period*

5.4.2.2 PI responses

The survey questionnaire was completed by PIs at 32 sites. Of the 30 sites that opened and recruited, a PI response was obtained from 27 sites. The PI at one site was on maternity leave when the survey was conducted and the survey questionnaire could not be sent to her. One site had two PIs and both had responded to the questionnaire, one response was selected at random to be included in the analysis of PI responses. Of the three sites that opened but did not recruit, a PI response was obtained from all three sites. Of the four sites that did not open to recruitment, PIs from two sites completed the questionnaire.

5.4.2.3 Research nurse responses

The survey questionnaire was completed by research nurses at 30 sites. Of the 30 sites that opened and recruited, a research nurse response was obtained from 28 sites. The survey could not be sent to research nurses at two sites as they had left post during the course of the trial. Of the three sites that opened but did not recruit, a research nurse was available at only one site and she responded to the questionnaire. There was no designated research nurse at one site and the research nurse at the other site had left post prior to the survey. Of the four sites that did not open to recruitment, only one site had a designated research nurse, who completed the questionnaire.

5.4.3 Response rates

The overall response rate to the survey was 39%. The response rates of principal investigators and at least one research nurse per site are presented in Table 16.

Table 15: Response rates for PIs and at least one research nurse per site

Sites	**Number of PIs**	**PI responses**	**Number of Research Nurses**	**RN responses (one per site)**
Sites that recruited (n=30)	29*	27 (93%)	28 [2α]	28 (100%)
Sites that opened but didn't recruit (n=3)	3	3 (100%)	1 [α,β]	1 (100%)
Sites that never opened (n=4)	4	2 (50%)	1 [3 β]	1 (100%)

*PI at one site on maternity leave
α RN had left post before the survey was conducted, μ No designated research nurse at site

5.4.4 Facilitators and barriers to recruitment

5.4.4.1 Overall responses

The facilitators and barriers to recruitment identified in overall responses are ranked in order of frequency and presented in Table 17.

Motivation and commitment of the study team was the most commonly identified facilitator to trial recruitment potentially offsetting the effects of practical constraints such as heavy clinical workload, shift patterns of work, lack of adequate number of trained staff and local clinical arrangements. Presence of a research nurse and a designated research team were thought to be very helpful in assisting busy clinical teams with trial recruitment and data collection.

Effective communication and coordination between study team members at site was recognised to be an important factor that helped recruitment. An experienced Principal investigator and enthusiastic clinical team with good communication skills were thought to be instrumental in resolving local problems and ensuring successful trial recruitment at sites. Clinical teams' perception of the importance of the research question and a positive attitude to involving patients in research was felt to be very important. Encouragement and support provided by PIs, senior clinicians and research nurses was important to keep up the motivation levels of staff and develop a positive research culture.

Trial management support and good communication between the Clinical Trials Unit and study team at site were recognised as facilitators. Internal trial publicity by the study teams helped to maintain the presence of MAGNETIC trial among teams and increase parents' and families' awareness about the trial.

Simple patient inclusion criteria and clear presentation of trial information boosted recruitment. Good communication between research teams and parents and consent seeking by experienced and trained clinicians was thought to be very helpful in overcoming barriers such as parental anxiety about the potential adverse effects of the trial drug and their child taking an experimental medication or placebo. However, some responders expressed discomfort in approaching patients for taking consent. Excessive amount and complexity of trial information and time taken to complete trial related administrative work were criticised. Additionally, language and cultural barriers were thought to hinder recruitment.

Another important hurdle was the time and setting of consent seeking. There was a 20 minute window period for taking informed consent while the patient was receiving initial treatment in the emergency department or children's assessment unit. Seeking consent from the parents of an ill child in an acute or emergency setting in 20 minutes was found to be very challenging by the clinical teams.

Lack of availability of research staff out of hours was recognised as an important barrier as these were noted to be times with excess patient flow but reduced staff, resulting in missing eligible participants for recruitment. An important regulatory hurdle identified by a high proportion of responders was Good Clinical Practice (GCP) training for clinical staff. Arranging GCP training and encouraging clinical staff to attend was found to be very difficult. Recruitment difficulties arising due to seasonal variation were also recognised.

Table 16: Facilitators and barriers to recruitment in order of frequency of responses

Facilitators	**(%)**	**Barriers**	**(%)**
Motivation of MAGNETIC study team at site	78.9	Clinical workload	87.3
Communication and coordination between study team members at site	74.5	Shift patterns of work	77.7
Communication skills of clinical team	70.3	Number of trained staff	77.3
Presence of designated research nurse/practitioner	68.1	Time and setting of consent seeking	76
Research experience of PI and study team members at site	63.3	GCP training	69.6
Publicity by the trial team	62.9	Time to complete administrative work related to the trial	66.6
Communication and coordination between study team at site and CTU	62.1	Parent's concerns about side effects of new drug	65.3
Trial management	62	Parent's attitude towards their taking experimental medicine or placebo	57.2
Clinician attitude to involving patients in research	60.9	Availability of research staff out of hours	57
Perceived importance of the particular research question	60.1	Difficulty in approaching patients for consent	53.9
Availability of designated research team	58.5	Local clinical arrangements	52.1
Clarity in presentation of trial information	58.4	Seasonal variation	51.8
Patient inclusion criteria	57.5	Language or cultural barriers	50.3
Motivation of clinical team	53.6	Amount and complexity of trial information provided	50
Experience and training of clinical team seeking consent	50.4		
Communication between research team and parents	50.4		

5.4.4.2 Principal investigator responses

The responses from the Principal investigators were also analysed separately. The facilitators and barriers to recruitment identified in responses from Principal investigators are ranked in order of frequency and presented in Table 18. The perception of Principal investigators was different from research nurses and overall responses in some respects. Motivation of the clinical team, their experience and training in providing information and seeking consent and communication between research team and parents were not recognised as facilitators. However, research experience of clinical team was thought to boost recruitment.

The principal investigators did not see parents' concerns about side effects of the drug or their anxiety related to their child taking experimental medicine, as barriers, which may be explained by their experience and skills in communicating with parents. This group did not find it difficult to approach patients for consent and language and cultural barriers were not perceived to be important. Information provided to parents or families was not felt to be excessive or too complex. However, a delay in opening of site was identified as a barrier by Principal investigators at more than 50% of the sites. This group regarded consent seeking by senior doctors and nurses as a hindrance to recruitment.

Table 17: Facilitators and barriers to recruitment in PI responses

Facilitators	**%**	**Barriers**	**%**
Motivation of MAGNETIC study team at site	80.7	Clinical workload	87.5
Communication and coordination between study team members at site	77.4	Shift patterns of work	84.4
Communication skills of clinical team	75	GCP training	84.4
Presence of designated research nurse/practitioner	68.8	Time and setting of consent seeking	81.3
Availability of designated research team	65.7	Number of trained staff	81.3
Patient inclusion criteria	64.5	Time to complete administrative work related to the trial	62.5
Perceived importance of the particular research question	62.5	Seasonal variation	62.5
Communication and coordination between study team at site and CTU	61.3	Availability of research staff out of hours	59.4
Research experience of PI and study team members at site	61.3	Senior doctors and nurses seeking consent	58.1
Publicity by trial team	59.4	Time to open up site	56.3
Trial management	59.4	Local clinical arrangements	54.8
Clarity in presentation of trial information	59.4		
Clinician attitude to involving patients in research	56.3		
Research experience of clinical team	53.1		

5.4.4.3 Research nurse responses

The perception of research nurses was also different in some respects, compared to overall responses and Principal investigator responses. They recognised some additional factors as facilitators such as presence of clinical equipoise, which was not identified in overall responses or by the PIs. This group perceived that recruitment was better if senior doctors and nurses sought consent.

They also identified some additional barriers. The clinical team was thought to be lacking in research experience and motivation, which hindered recruitment. Research was not perceived to be important in routine clinical practice and the local research culture was felt to be unhelpful. They identified additional practical constraints such as data collection and trial demands resulting from study protocol being different from routine clinical practice. It was felt that recruitment was hindered by the fact that MAGNETIC was a drug trial and parents were not familiar with the experimental medicine resulting in a low consent rate.

The research nurse responses ranked in order of frequency are presented in Table 19.

Table 18: Facilitators and barriers to recruitment in research nurse responses

Facilitators	%	Barriers	%
Communication and coordination between study team at site and CTU	90	Clinical workload	93.3
Trial management	82.8	GCP training	86.7
Publicity by trial team	75.9	Number of trained staff	83.3
Motivation of MAGNETIC study team at site	73.3	Shift patterns of work	83.3
Communication and coordination between study team members at site	73.3	Time and setting of consent seeking	76.7
Research experience of PI and study team members at site	70	Research experience of clinical team	76.7
Communication between research team and parents	70	Parent's concerns about side effects of new drug	76.7
Patient inclusion criteria	66.7	Local research culture	73.3
Clarity in presentation of trial information	66.7	Local clinical arrangements	70
Presence of designated research nurse/practitioner	65.5	Data collection process	66.7
Communication skills of clinical team	63.3	Availability of research staff out of hours	63.3
Availability of designated research team	60	Perceived importance of research generally in clinical practice	63.3
Clinician attitude to involving patients in research	60	Parent's attitude towards their taking experimental medicine or placebo	62.1
Perceived importance of the particular research question	53.3	MAGNETIC being a drug trial	62.1
Senior doctors and nurses seeking consent	53.3	Time to complete administrative work related to the trial	60
Experience and training of clinical team seeking consent	53.3	Seasonal variation	60
		Familiarity with experimental treatment	60
		Motivation of clinical team	56.7
		Consent rate	56.7
		Study protocol compared to clinical practice	56.7
		Language or cultural barriers	53.3
		Difficulty in approaching patients for consent	50
		Choice of recruitment setting	50

5.4.4.4 Differences in perception of PIs and research nurses

Some additional facilitators and barriers identified only by the principal investigators or the research nurses have been mentioned previously. There were also differences in opinion between PIs and research nurses in some of the domains as to whether they were facilitators or barriers. In 15 (55%) sites there was a difference of perception as to the impact of the experience of the research team on study success. 53% of PIs perceived this as a facilitator, whereas 77% of the research nurses regarded this as a barrier. In 12 (46%) sites, there was a difference in perception of the impact of senior clinicians and nurses seeking consent on ease of recruitment. 58% of PIs regarded this a barrier, whereas 77% of the research nurses regarded this as a facilitator.

5.4.5 Correlation of PI responses with calibrated site recruitment

Scatter charts were initially plotted for each factor against calibrated site recruitment to examine a possible relationship between the two variables. These are presented in Appendix 22. Spearman's rank-order correlation was calculated to measure the strength and direction of association between each factor and calibrated site recruitment. A positive correlation, indicating an increase in calibrated site recruitment with increase in PIs score for the factor and vice-versa, was noted with trial design (r_s 0.462, p 0.031), MAGNETIC being a drug trial (r_s 0.488, p 0.021), trial management (r_s 0.46, p 0.031), choice of recruitment setting (r_s 0.504, p 0.017), consent rate (r_s 0.553, p 0.008), parent's attitude towards their child taking experimental medicine or placebo (r_s 0.639, p 0.001), language or cultural barriers (r_s 0.426, p 0.048), research experience of clinical team (r_s 0.428, p 0.047), presence of designated research nurse/practitioner (r_s 0.442, p 0.04),

difficulty in approaching patients for consent (r_s 0.582, p 0.004), communication and coordination between study team at site and CTU (r_s 0.507, p 0.019). A negative correlation, indicating an increase in calibrated site recruitment with decrease in the PIs score for the factor and vice-versa, was noted with competing local research projects, which was statistically significant (r_s -0.473, p 0.026).

Univariate regression analysis was conducted and factors listed below were found to be significant predictors of calibrated site recruitment. The sample size was inadequate for the number of independent variables, to be able to conduct a multivariate analysis, since the data on PI responses and calibrated site recruitment was available only for 22 sites (Wilson VanVoorhis 2007). The assumption of a normal distribution for calibrated site recruitment was felt to be reasonable, although a slight skew was noted (Appendix 23).

- MAGNETIC being a drug trial (R^2 0.2, p-value 0.037)
- Choice of recruitment setting (R^2 0.23, p-value 0.026)
- Competing local research projects (R^2 0.19, p-value 0.042)
- Consent rate (R^2 0.29, p-value 0.01)
- Parent's attitude towards their child taking experimental medicine or placebo (R^2 0.41, p-value 0.001)
- Language or cultural barriers (R^2 0.21, p-value 0.031)
- Difficulty in approaching patients for consent (R^2 0.27, p-value 0.013)
- Amount and complexity of trial information provided (R^2 0.18, p-value 0.049)
- Communication and coordination between study team at site and CTU (R^2 0.25, p-value 0.021)

These results are presented in Appendix 24.

5.4.6 Recruitment strategies

Free text responses were received from 108 participants on interventions or strategies that were applied to overcome the barriers to recruitment. Having a designated research nurse was the most commonly reported intervention (25%). Research nurses were found to be very helpful at all stages of recruitment; from identification of potential patients to notifying staff, helping with trial procedures and data collection and providing hands on support to the busy clinical teams. They were involved in providing training to staff and were thought to be instrumental in bringing about a change in culture at sites; motivating staff to be more involved and to recruit to the trial. Presence of Medicines for Children's Research Network (MCRN) clinical research facilitators was thought to be helpful in reminding staff about the trial. 10 responders commented on the effectiveness. Responders described presence of a research nurse as 'critical', 'essential to the success of the trial' and 'very effective'. One site attributed its success to appointment of a paediatric research nurse who was described to have 'generated enthusiasm in the clinical team', 'made protocol violations extremely unlikely through education and reminders', leading to a 'dramatic improvement in recruitment'.

GCP training was the second most commonly reported strategy (20.4%). Training sessions were arranged and doctors were encouraged to undertake GCP training. Four responders commented on the practical aspects of conducting the training and found it to be challenging, 'hard to maintain' and difficult to train all doctors due to practical constraints such as heavy workload, short term sickness and high

rate of turnover of doctors. One responder commented on the effectiveness and found it to be very effective. One responder suggested that GCP training should be incorporated as a part of the core training for paediatric registrars. Additional funding to encourage GCP training was suggested by another.

Teaching and training of staff was the next most commonly mentioned intervention (19.4%). Responders reported ‘multiple teaching and training activities’ and ‘roll out programmes’ to ensure that the staff were up to date with the study and could answer parents’ or patients’ questions with ease, follow the protocol and perform the asthma severity scoring accurately. Refresher sessions were provided to keep the staff trained during periods of no recruitment due to seasonal variation. Efforts were made to train most staff, so that a trained member of staff was available on most shifts. Training sessions were arranged for both doctors and nursing staff. One responder suggested training more nursing staff than doctors, due to rotational posts and frequent changeover of doctors. Only two responders commented on the effectiveness, who found this intervention to be very helpful and effective.

Trial publicity was mentioned next (10.2%). Posters were put up in the ward and clinical areas to remind the parents, patients and clinical teams about the trial. Responders mentioned putting up posters across the hospital and ‘frequent change of posters to remind staff and attract attention’. Recruitment graphs were displayed and emailed to staff with praise for recruiting to the trial. One responder mentioned that a variety of ‘aide memoires’ were placed throughout the department such as ‘MAGNETIC was go’; ‘Got a wheeze? Think MAGNETIC’. The trial was reported to be promoted via notice boards, memo books and

publicised during teaching sessions. Two responders commented on the effectiveness and found it to be effective.

Motivation and support provided by principal investigator and senior medical team (10.2%) was thought to play a very important role. Senior medical staff made themselves available and accessible to offer advice and practical help with recruitment. Regular communication with staff was felt to be important (8.3%). 'Regular updates and presentations at staff meetings to raise and maintain the profile of the study in the department' were reported. Regular meetings and discussions with the team were thought to be very effective in increasing awareness about the trial and improve recruitment, 'despite initial hindrances from the nurses and clinicians'. Repeated reminders to clinical staff (4%) emphasizing the importance of identification and recruitment of patients was mentioned.

Measures to improve availability of doctors and research nurses (4.6%) to screen and consent were taken. Up to date list of people who could recruit and their contact details were made available to ward staff. Making a rota of prescribing doctors, giving bleeps to doctors and having an onsite doctor for screening and consent were mentioned. Research nurses were mobilised to be more available and to help with trial recruitment. Additional support measures during out of hours (4.6%), such as extra staff and twilight nurses and the funding to support this, was arranged. One responder mentioned limiting trial recruitment to office hours when more staff was available.

Efforts were made to encourage clinical staff to recruit and to be more involved in the trial adding a competitive edge but staff attitudes were found to be very

difficult to change (4.6%). Motivated nursing staff in A&E who could identify patients and inform the research team was found to be effective in improving recruitment. Incentives were offered to staff for identifying and recruiting patients (3.7%), which was found to be effective. Good communication and improved relations between teams was found to be helpful. Recruitment and consent by senior and more experienced members of the team was felt to be very important as 'seeking consent in the acute setting where treatment needs to be initiated ASAP', was thought to 'put parents and clinical teams under pressure'. CTU support and having a dedicated trial manager was found to be very effective.

Other measures that were taken were to ensure GCP trained staff at every shift which was reported to be not always possible. Nurse practitioners were encouraged to prescribe the drug and recruit patients. Shorter and simpler trial instructions and simpler paperwork were tried. Data collection was made simpler by giving the nursing staff fewer pages of the CRF. Clinical staff was encouraged to collect data that was needed at the time and research nurses collected demographic and other data retrospectively. Weekly screening was found to be useful to track if any patients were being missed. Medical staff was chased for reasons for missing eligible patients.

5.4.7 Free text responses on organisation of MAGNETIC

The importance of having a designated research nurse at every centre was emphasized. It was felt that research nurses should be available to help with recruitment particularly at busy times and out of hours when more eligible patients came in and were missed due to heavy clinical workload. Availability of a

designated research nurse was described as ‘single most significant facilitator to recruitment and completion of the protocol in a timely manner’.

Difficulties in seeking consent from parents of an acutely unwell child in 20 minutes was reported to be very difficult and there were suggestions about increasing the recruitment window period and taking out the 20 minute time limit to consent. Responders recognised that there was no easy solution to seeking consent from parents in the acute situation but also felt that they got better as more patients were recruited to the trial. One responder suggested the option of introducing ‘emergency department criteria for consent’, whereby consent could be taken quickly using the patient summary sheet only and going through the whole information document once the trial had started. He/she felt that the experimental drug was a ‘known’ drug and that parents were always told about the option to discontinue from the study at any time, if they wished to. Another responder mentioned deferred consent.

Training of medical and nursing staff to participate in the study was felt to be important. It was thought that junior doctors at the SHO level should be trained to seek consent and recruit patients, so that the middle grade doctors and registrars were less restricted. It was thought to be important to train staff in both A&E and paediatric wards and that research nurses in A&E be trained to recruit independently. Providing training sessions at new doctors’ induction and regional training was suggested.

Having GCP trained staff available to recruit was thought to be very important. There were suggestions about making study leave available for GCP training, making it mandatory during registrar training and to have nationwide GCP

training sessions provided by CTU, for A&E doctors. However, encouraging doctors to attend GCP was felt to be a big hurdle as it was seen as ‘boring’, ‘time consuming’ and ‘not a priority for busy clinicians’.

The need to encourage and motivate doctors and nursing staff to recruit and be more involved in the trial was recognised. Trainee doctors were reported to lack interest in research. The need to ‘change the research culture’ and ‘move towards a general ethos of research being an integral part of clinical practice’ was emphasized. Suggestions were made to simplify the trial protocol and wording of the parent information leaflets. Data collection was thought to be too complex and time consuming and the need to minimise data collection was recognised, making it simpler and easier to collect.

There were suggestions to improve the staffing levels particularly during out of hours with more doctors and nursing staff available to consent. There was a suggestion for research nurses to be available out of hours, as these were noted to be the busiest periods, when eligible patients presented and were missed as the ability to recruit them was determined by the clinical workload. Greater involvement of senior medical staff such as consultants was also recommended during these times.

Recruitment over a long period of time was felt to be unhelpful in the A&E setting and preference was expressed for shorter, heavily resourced periods of recruitment in the asthma season. A selection of ‘fewer centres’, with track record for recruitment was recommended to ‘prevent dissipation of resource and effort across too many sites’. In-depth feasibility assessment to assess the suitability of site, setting and clinical teams was thought to be essential.

The choice of recruitment setting was highlighted by a few responders who felt that recruitment should have been done in A&E rather than the paediatric ward as patients were no longer eligible for the study by the time they reached the ward because of geographical distance or due to the treatment they had received in A&E. A preference for having an A&E consultant as the PI was expressed by a few responders. Adequate funding for the trial to be able to fund a research nurse at every site and twilight nurses, was thought to be important. Per patient funding was reported to be useful drivers and motivators for the team.

Trial publicity by putting up posters in A&E and clinical areas, waiting rooms, and distributing leaflets to parents was thought to be helpful in increasing the consent rate and to 'dampen fear of parents'. Development of the role of nurse practitioners and non-medical prescribers in research was encouraged. Lack of communication of challenges and counter strategies between sites and the need for better communication was acknowledged. Other suggestions included a faster set up process, better availability of study drug and greater number of study co-applicants.

The study was thought to be very well organised by some responders. The success of the trial at sites was attributed to factors such as motivation and hard work of clinical staff, motivation of PI and nursing staff and presence of a designated research nurse. The trial manager was reported to be 'excellent' and 'fantastically supportive'.

5.5 DISCUSSION

This study explored the recruitment experience of the clinical teams involved in recruitment to the MAGNETIC trial at various sites. The responders endorsed the various facilitators and barriers to recruitment to clinical trials that have been identified in existing literature. Motivation of the clinical team, good communication skills, research experience of PI and clinical team, good trial management, research nurse support, positive research culture and effective communication between teams and with patients have been recognised as important factors that boost recruitment (Campbell et al. 2007). Time constraints of clinicians, heavy clinical workload, shift patterns and training and staffing issues have been recognised as important hindrances to recruitment (Ross et al. 1999).

The clinical teams recognised parents' apprehension about their child taking an experimental medicine and their concerns about the potential adverse effects as barriers, which have been previously described as important considerations for parents when deciding for their child to participate in clinical trials (Caldwell, Butow & Craig 2002). Paediatricians have been found to consider trial participation as an additional burden for parents and practitioners express discomfort in approaching patients for research (Shilling et al. 2011). Our study reiterates the need for mentoring and providing training and support to clinicians. Excess amount and complexity of trial information provided in the patient information leaflets, has been previously criticized similar to the findings in this survey.

This study highlights research nurse support and presence of designated research teams particularly out of hours, as very important. Having a designated research nurse was the most commonly reported intervention for improving recruitment. Another factor to note is GCP training, which has been described as a 'massive hurdle'. Engaging doctors to undertake GCP training was found to be very difficult and described as 'time consuming, boring and not a priority for busy clinicians'. The study highlights some differences in perception of principal investigators and research nurses with regards to certain facilitators and barriers to recruitment, which may be useful to keep in mind when planning future trials.

An important trial specific barrier was seeking consent from the parents of an ill child in 20 minutes, which raises the issue of an option of deferred consent being available for paediatric trials in acute or emergency settings. The UK law incorporates a deferred consent process in emergency situations for minors (Legislation.gov.uk 2008) when treatment is required urgently, urgent action is required for the purposes of the trial, consent cannot be obtained prospectively and the procedure has been approved by the ethics committee. A postal survey (Gamble et al. 2012) investigating parents' views about deferred consent in a paediatric emergency setting showed that majority of parents found it acceptable. However, death of a child during a trial in which deferred consent has been used presents a complex situation and the authors highlight the need for further evidence to guide appropriate management in these cases.

This study highlights several important factors that affect recruitment to clinical trials. The strengths of our study include an electronic survey design using an

evidence based recruitment survey tool, wide range of responders with different roles from sites with variable recruitment performance and high response rates from PIs and research nurses. E-surveys are quicker, less expensive, can be sent to multiple responders at the same time, avoid interviewer bias and the responders have the opportunity to express their views freely and anonymously, even to sensitive issues (Wiley 2008).

Responses from a range of responders with different roles and sites with different recruitment performance increased the breadth of data gathered in terms of recruitment experience and perspectives, increasing the generalizability of the results. A high response rate from the PIs and at least one research nurse from each site ensured equal representation of sites in overall responses, thereby ensuring generalizability and avoiding selection and non-respondent bias.

Our study was designed to be free of the threats to validity and quality issues identified in a review of previous studies (Fayter, McDaid & Eastwood 2007). The survey questionnaire was sent to all staff involved with trial recruitment at all sites irrespective of recruitment performance, to avoid selection bias. The survey instrument used in the study provided an evidence-based comprehensive list of potential factors affecting recruitment for responders to rate as facilitators or barriers. Additional free text comments were invited to capture their experiences and views on ways of improving recruitment to the trial. The method of developing and administration of the survey, data collection and analysis and the study results have been reported clearly.

The study has some potential limitations. The survey questionnaire has the disadvantage of respondent non-response, misinterpretation of questions, or selective responder bias. We tried to overcome these limitations by wording the questionnaire in simple and clear language and piloting the questionnaire prior to use. Frequent e-mail reminders were sent out and extra efforts were made to seek responses from PIs and research nurses at each site.

The overall response rate to the survey was 39% but this was not a true representation of the actual response rate. The denominator included all contacts whose email addresses were available from the delegation logs and it is likely that not all contacts would have received the survey, if their email address had changed and were different at the time the survey was conducted. There was a high likelihood of people changing jobs or rotating between different NHS trusts during the two year duration of the trial, particularly doctors in training, nursing staff and other junior doctors, resulting in a change in their email address and contact details. This was pre-empted during the planning stage of this study and extra efforts were made to receive a response from the principal investigator and at least one research nurse per site.

The results of the survey are based on subjective experiences of clinical staff who responded to the survey questionnaire. We tried to overcome this limitation by achieving a good representation of sites in overall responses and analysing PI and at least one research nurse response at each site separately. We looked for co-relation between PI responses and calibrated recruitment at sites but this analysis was limited by non- availability of data. Data on the number of 2-16 year old

patients at each site was not available. The number of 2-16 year olds presenting to AE at the trust level was used a proxy indicator of the eligible population and this information was available only for the English sites.

This study presents the recruitment experience of the clinical teams recruiting to the trial; understanding the perspective of other stakeholders such as parents, young people and families is also very important.

5.6 SUMMARY & CONCLUSIONS

This study explored the recruitment experience of various clinical teams recruiting to the MAGNETIC trial and identified important perceived facilitators and barriers and information on strategies adopted by clinical teams to boost recruitment. The findings of the study can be generalised to other trials particularly in the acute/emergency setting as it helped to identify generic facilitators and barriers that operate in these settings along with trial specific factors. The responders emphasized the importance of having motivated and enthusiastic clinical teams, good communication skills and a positive research culture. Good trial management, trial publicity, encouraging clinical staff to participate and constant efforts to keep up the momentum of the trial are important. The study recognises practical problems encountered by the clinical staff in acute and emergency settings and stresses on the presence of designated research teams and research nurse support particularly out of hours, to boost recruitment. Reducing data collection and administrative work related to the trial are recommended. GCP training is seen as a major hurdle and there is an emphasis on increasing the provision of training sessions and encouraging doctors

to attend training. Difficulties in seeking consent in a short time period in the emergency setting highlights the need to consider the option of deferred consent in future clinical trials with sick children in the emergency setting. The study acknowledges parents' concerns and apprehensions about trial medication and their child's participation in a trial; therefore provision of simple and clear information by trained staff is recommended.

This study has generated valuable information on facilitators and barriers to recruitment to clinical trials and highlighted some recruitment strategies applied by the clinical teams to overcome the hurdles. The findings of this study can be used to inform the design and conduct of future clinical trials. It is recommended that trialists should consider using study designs with simpler protocols which are comparable to routine clinical practice, the inclusion criteria being less restrictive and data collection being not too excessive. Designated research nurses should be made available at sites to assist clinical staff with recruitment particularly during out of hours. This is particularly applicable to trials in the acute or emergency setting with heavy clinical workload. The option of deferred consent should be considered for trials in the emergency setting. Clinical staff should be encouraged to undertake GCP training and efforts should be made to motivate doctors and nursing staff to participate in research. Adequate training should be provided to doctors to enhance their confidence and skills in communicating with parents and families, seeking informed consent and allaying their concerns about the trial or experimental medicine. Patient information leaflets should be kept short and information should be provided in a simple and clear manner. Trial publicity measures such as posters and banners should be put up to maintain awareness of

trial among staff and patients. Central trial management support should be provided and efforts should be made to ensure effective communication between clinical teams at various sites.

Chapter 6

DISCUSSION

6.1 KEY FINDINGS WITH REFERENCE TO OBJECTIVES

The work contained within this thesis presents some important findings in relation to the research objectives. These findings are discussed below, in the context of existing knowledge.

Objective 1: To determine the recruitment performance of randomised controlled trials with children

The review of recruitment to randomised controlled trials with children in the NIHR portfolio, described in chapter 3, confirmed that under-recruitment and recruitment delays are significant problems in paediatric trials. Overall, 69% of included trials recruited to target but only a third of the UK based paediatric randomised controlled trials recruited to target within the stipulated time frame or in a period not exceeding ten percent of the planned recruitment period. Nearly half of UK studies had to apply for a trial extension and the recruitment target needed to be revised in just under a quarter. Recruitment was discontinued earlier than planned in seven percent of trials because of problematic recruitment. These findings are congruent with reviews of recruitment to multicentre RCTs with adults (Campbell et al. 2007, Sully, Julious & Nicholl 2013). Sully et al report failure to meet recruitment targets in 45% of studies with revision of target needed in 19% and trial extension in 47%, which shows an improving trend over time, compared to findings of Campbell et al. However, these reviews pertain mainly to

adult RCTs whereas our study reviewed recruitment to exclusively paediatric trials.

The pilot systematic review, described in chapter 2, aimed to determine the recruitment performance of paediatric trials in published literature. The study showed that reporting of recruitment and consent in paediatric RCTs was poor and it was not possible to obtain unbiased estimates of percentage of total recruitment achieved and consent rate from published literature.

Objective 2: To test the association of potential factors that influence recruitment to paediatric randomised controlled trials with recruitment success

The review of paediatric RCTs in the NIHR portfolio showed that presence of a dedicated trial manager was significantly associated with recruitment success. 76.7% of trials with a dedicated trial manager recruited successfully compared to 40% trials without a dedicated trial manager (p-value 0.015). The importance of good trial management is well recognised. Efficient trial management is considered to be one of the key components required to deliver high quality trials and it is thought that many trials fail because of the 'lack of a structured, business-like approach' to trial management (Farrell, Kenyon & Shakur 2010). The MRC recognises that some trials fail due to problems with trial management rather than scientific reasons or problems with trial design (Clinical Trials for Tomorrow, 2003). The STEPS study (Campbell et al. 2007) found that trials with a dedicated trial manager were more likely to recruit successfully but the confidence interval was wide and this was not statistically significant (OR 3.8, 95% CI 0.79-36.14, p-

value 0.087). However, the authors discuss that the analyses testing the association of factors and recruitment success were of limited value because of imprecision around the estimates and lack of sufficient power to undertake a multivariable analysis.

Other factors such as being an IMP vs. non-IMP trial, trial of acute vs. chronic illness, having CTU involvement, pilot/feasibility study and additional trial demands were not found to have a significant association with recruitment success. Studies with a pilot/feasibility assessment and CTU involvement were more likely to recruit successfully but the results were not statistically significant. This could be explained by confounding factors such as trial complexity in that simple and easy to recruit studies may not have had a pilot/feasibility study or CTU involvement compared to more complex trials. Sully et al reported that trials with CTU involvement recruited better than trials without CTU involvement but the results were not statistically significant (Sully, Julious & Nicholl 2013).

There is paucity of data on factors that are associated with recruitment success in paediatric trials. Studies show that parents assess the risks and benefits of trial participation and take the practical aspects and inconvenience resulting due to trial participation into consideration, when taking a decision about their child's participation in clinical research (Harth, Thong 1995, Langley et al. 1998, Hayman et al. 2001, Shilling et al. 2011). Our study did not find a significant association with additional trial demands and recruitment success though certain trends were noted. Trials recruited better if routine data collection was carried out and an additional test or procedure was offered but less well if an extra hospital

visit or extended hospital stay was involved. A bigger study with greater power may be needed to detect a significant association between the two.

Objective 3: To identify facilitators and barriers to recruitment of children to a multi-centre RCT and strategies adopted by clinical teams to overcome barriers

The survey of clinical teams recruiting to the MAGNETIC trial, described in chapter 5, identified the important facilitators and barriers to recruitment. A motivated clinical team with effective communication between team members and with parents, effective coordination between study team members at site and between sites and CTU, trial management support, presence of a research nurse and availability of a designated research team to help with recruitment were considered imperative for trial recruitment success. Research experience of PI, clinical teams' perception of the importance of the research question, their attitude to enrolment of children in clinical trials and internal trial publicity were thought to be important facilitators. Simple inclusion criteria and clarity in presentation of trial information to parents were thought to help recruitment. These findings are consistent with the existing literature on facilitators identified in adult studies (Campbell et al. 2007).

Heavy clinical workload, shift patterns of work, lack of trained staff particularly out of hours and local clinical arrangements were recognised as barriers to recruitment. Arranging GCP training and encouraging doctors to attend was identified as a problem. Parents were anxious about the side effects and safety of experimental treatment. Language and cultural barriers were recognised and the

amount and complexity of trial information was criticised. Seasonal variation was noted to hinder recruitment. These barriers to recruitment have been identified in existing literature on adult studies (Fayter, McDaid & Eastwood 2007).

However, as discussed, the evidence on facilitators and barriers to recruitment to paediatric trials is limited and the existing literature is mostly confined to studies of adult recruitment (Prescott et al. 1999, Ellis 2000, Cox, McGarry 2003, Tournoux et al. 2006, Mills et al. 2006, Fayter, McDaid & Eastwood 2007). A study examining paediatricians' attitudes towards RCTs with children found poor parental awareness of concepts such as random allocation, placebo usage and equipoise and thought that parents' willingness to participate was influenced by their opinions. Parents were thought to be apprehensive regarding experimentation on their children (Caldwell, Butow & Craig 2002). Random allocation, clinical equipoise and clinician influence were not identified either as facilitators or barriers in our study. However parents' concerns about adverse effects of new treatments and their anxiety around their child having an experimental treatment or placebo were recognised. Language and cultural barriers were also identified, which is consistent with findings of Caldwell et al. Paediatricians are known to believe that parents would be less likely to participate in trials if their child's condition is severe (Walterspiel 1990, Caldwell, Butow & Craig 2002). Clinical teams in our study expressed difficulty in seeking consent from parents of an acutely unwell child particularly in a limited time frame and suggestions were made for consideration of deferred consent in recruiting children from an emergency setting. Making trial participation more convenient for parents has been noted to increase trial participation (Caldwell, Butow & Craig 2002).

However, additional trial demands were not identified as a barrier in our study since this trial did not entail any extra blood tests, clinic visits or extra travel. The amount and complexity of trial information provided were criticised in line with existing research (Shilling et al. 2011).

The commonly reported strategies adopted by clinical teams to boost recruitment were to have a designated research nurse, GCP training, trial related training of staff and regular communication, motivation provided by senior staff, trial publicity, measures to improve availability of clinical staff particularly out of hours and giving incentives to staff. A systematic review of studies that evaluated the recruitment activity of clinicians identified strategies such as use of qualitative research to identify and overcome barriers to recruitment, reduction in clinical workload, provision of extra training and protected research time to be effective strategies.

6.2 CONTRIBUTION TO EXISTING LITERATURE

This section summarises the contribution of this thesis in advancing knowledge about recruitment of children to randomised clinical trials.

6.2.1 Recruitment of children to randomised clinical trials

While there is available knowledge about recruitment of adults (Campbell et al. 2007, Sully, Julious & Nicholl 2013), there is very little existing knowledge about recruitment of children to clinical trials and the scale and magnitude of the problem is not known. To the best of our knowledge, this thesis is the first to provide quantitative estimates of recruitment performance of a cohort of

exclusively paediatric randomised controlled trials and test the association of potential factors affecting recruitment with recruitment success.

6.2.2 Facilitators and barriers to recruitment to randomised clinical trials with children

An evidence-based online survey tool has been developed, as described in chapter 4, to establish the recruitment experience of clinical teams with regard to the perceived facilitators and barriers to recruitment, to identify strategies applied to overcome the barriers and to obtain suggestions for change in organisation of future trials. There is no such existing recruitment survey tool to the best of our knowledge. It can be a useful instrument for the systematic recognition and management of recruitment problems in clinical trials and generate knowledge to inform the design and conduct of future trials.

The survey of clinical teams recruiting to the MAGNETIC trial has provided important generic and trial specific information about the facilitators and barriers to recruitment that can be generalised to other paediatric trials and to trials recruiting acutely unwell children in the emergency setting.

6.3 IMPLICATIONS FOR PRACTICE

Several conclusions can be drawn from this thesis which has implications for clinical trialists undertaking research with children and provide guidance on how clinical trials should be designed, planned and conducted in the future.

6.3.1 Planning and designing clinical studies with children

With increased recognition and acceptance of the importance of conducting clinical trials with children, it is imperative that clinical trials be planned, designed and conducted in a manner that maximises the potential for successful completion of the trial in the given budget and time frame. A clinically important and interesting research question that is relevant to clinical practice is more likely to engage the clinical teams to participate. Keeping the study protocol simple and more aligned to existing clinical practice is important to ensure adherence to protocol. Studies with less restrictive patient inclusion criteria and minimal additional demands on children, young people and their families are more likely to be easier to recruit.

A dedicated trial manager is very important for successful trial recruitment. Previous pilot/feasibility study with careful assessment of sites and settings for recruitment may help to pre-empt potential issues and problems with recruitment that can be addressed early on. CTU involvement can be very helpful at all stages and help with study design, trial management, identification and liaison with sites, planning staffing, randomisation, trial monitoring, data management and conducting the analysis.

6.3.2 Trial conduct

It can be concluded with confidence that efficient trial management and presence of a dedicated trial manager is crucial for successful recruitment. Communication and coordination between study team members at site and between site and CTU are important for identification and resolution of any problems that may be

encountered. Local clinical arrangements need to be conducive to conducting the trial successfully and appropriate number of trained staff should be available. Heavy clinical workload and shift patterns of work are recognised barriers but efforts must be made to ensure adequate staffing levels and presence of support staff to help with recruitment. Presence of a research nurse and a designated research team are thought to be extremely helpful in assisting the busy clinicians with recruitment especially during out of hours. Arranging trial specific training sessions for staff including GCP training have been shown to be useful. Measures such as regular meetings with staff and internal trial publicity using posters are important to keep the clinical teams motivated and maintain the presence of a clinical study. Trial slogans and posters in waiting areas and clinics also help raise parents' awareness about the trial. Efforts must be made to minimise the administrative work related to the trial and excessive data collection should be avoided.

6.3.3 Information and consent

Parents' anxiety about trial participation and use of experimental medicine or placebo needs to be acknowledged and efforts should be made to allay their apprehension. Good communication between research teams and parents is imperative to help parents understand the purpose of the research and enable them to make an informed decision about their child's participation in the study. Trial information should be provided in a simple and clear manner and efforts should be made to keep the patient information leaflets short and user-friendly. Given the importance of clear communication with parents and expressed discomfort of

clinicians in seeking consent, training and support should be offered to clinical teams. The option of deferred consent should be made available to trials in the emergency setting.

6.3.4 Trial monitoring and sharing good practice

The recruitment survey tool can be used as a trial monitoring tool to systematically record the facilitators, barriers and strategies applied at individual sites. Sharing this information between sites in a multicentre RCT can provide useful learning lessons and strategies to overcome barriers. The tool can be adapted for use after trial completion to generate knowledge that can influence future research with children.

6.4 CONCLUSION AND FUTURE RESEARCH DIRECTION

The thesis highlights a number of potential avenues that can be explored in future research studies. The results of the review of paediatric RCTs in the NIHR portfolio suggest possible association of pilot/feasibility study, CTU involvement and additional trial demands with recruitment success but the results were not statistically significant. A larger study with greater power is needed to detect the effect of these variables with certainty. While this study reviews the recruitment to exclusively paediatric trials, there is a need to examine recruitment to trials with both adults and children.

Survey of clinical teams recruiting to the MAGNETIC trial generated useful knowledge on facilitators and barriers to recruitment and strategies applied. The effect of these interventions such as having a designated research team, additional

trial specific training and GCP training for clinical teams, trial publicity measures like posters and incentives to staff can be tested further and validated by conducting nested trials of these interventions within an RCT setting. The effect of deferred consent on recruitment to trials with acutely ill children in the emergency setting needs to be evaluated.

Use of the recruitment survey tool by clinical teams can lead to systematic recording of data on facilitators and barriers to recruitment, resulting in a build-up of literature on the same in paediatric trials and help identify useful strategies. The recruitment survey questionnaire, published in Trials (Kaur, Smyth & Williamson 2012), has been adapted for use in trials to elicit barriers and facilitators to recruitment (Kaur et al. 2013, Kaur et al. 2013, Keightley et al. 2014). To date, the article has been accessed 5141 times on Bio Med Central site, cited by 17 papers (Appendix 25) and we have been contacted by six researchers (Appendix 26) to seek permission to use the questionnaire. The identified strategies can be further evaluated for effectiveness by conducting nested trials of interventions within RCTs.

The review of published literature revealed poor reporting of recruitment and consent and the limitations of using this approach to determine the recruitment performance of paediatric RCTs have been discussed previously. We recommend that the highlighted issues be taken into consideration by other researchers prior to using this method. Further work is needed to ensure adequate reporting of paediatric RCTs. The CONSORT statement provides an evidence-based minimum set of recommendations to facilitate clear and transparent reporting of RCTs. It

includes recommendations on reporting of flow diagram, sample size and recruitment (CONSORT 2010). The CONSORT-C guidance is being developed as an extension of the CONSORT to develop an evidence-based checklist of items to be included when reporting paediatric randomised controlled trials (Equator network- CONSORT C). Studies to assess the impact of the CONSORT statement on paediatric randomised controlled trials and their adherence to it will be important in bringing about an improvement in reporting of paediatric trials.

6.5 KEY MESSAGES

- Recruitment to randomised controlled trials with children is challenging. Poor recruitment and recruitment delays are a common problem.
- Trial management is significantly associated with recruitment success in paediatric RCTs. Trials with CTU support and pilot/feasibility assessment are more likely to recruit but further work is needed.
- Reporting of recruitment and consent in paediatric trials is poor and needs improvement.
- An online recruitment survey tool has been developed which can be used to investigate the recruitment experience of clinical teams. This can be used by trialists to systematically monitor recruitment to an on-going trial or gather information that can be used for conducting future trials.
- A survey of facilitators and barriers to recruitment to a large, multicentre randomised controlled trial with children in the emergency setting found some important generic and trial specific facilitators and barriers to recruitment and strategies that were applied to overcome the barriers. This

information can be used by trialists in planning and conducting future trials with children.

6.6 DISSEMINATION OF RESEARCH FINDINGS

The findings of this thesis will be disseminated through publication in peer-reviewed journals. The recruitment survey tool has been published in Trials (Kaur et al 2012). The review of recruitment to paediatric trials on the NIHR portfolio, described in Chapter 3, was presented as a poster presentation at the 2nd clinical Trials Methodology Conference, UK and will be sent for publication. The survey of facilitators and barriers to recruitment to the MAGNETIC trial, described in Chapter 5, was presented at the 2nd Clinical Trials Methodology conference, UK and is being drafted for publication. Other potential dissemination strategies include podcasts on the NIHR website highlighting the key findings.

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APPENDICES

Appendix 1: Search strategy used in the pilot systematic review of recruitment and retention of children in randomised controlled trials, as described in Chapter 2

CENTRAL was searched in January 2011 for clinical trials using the following search strategy:

#1 Infant [MeSH]

#2 Infant*

#3 Infancy

#4 Newborn*

#5 Baby*

#6 Babies

#7 Neonat*

#8 Preterm*

#9 Prematur*

#10 Postmatur*

#11 Child[MeSH]

#12 Child*

#13 Schoolchild*

14 Schoolage

#15 Preschool*

#16 Kid*

#17 kids

#18 Toddler*

#19 Adolescent [MeSH]

#20 Adoles*

#21Teen*

#22 Boy*

#23 Girl*

#24 Minors [MeSH]

#25 Minors*

#26 Puberty[MeSH]

#27 Pubert*

#28 Pubescen*

#29 Prepubescen*

#30 Pediatrics[MeSH]

#31 Pediatric*

#32 Paediatric*

#33 Peadiatric*

#34 Schools[MeSH]

#35 Nursery school*

#36 Kindergar*

#37 Primary school*

#38 Secondary school*

#39 Elementary school*

#40 High school*

#41 Highschool*

#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41

Appendix 2: Data extraction form used in pilot systematic review described in Chapter 2

Name of trial:

Source (Journal):

Author:

Year:

Flow Diagram: Y/N

Sample size calculation: Y/N

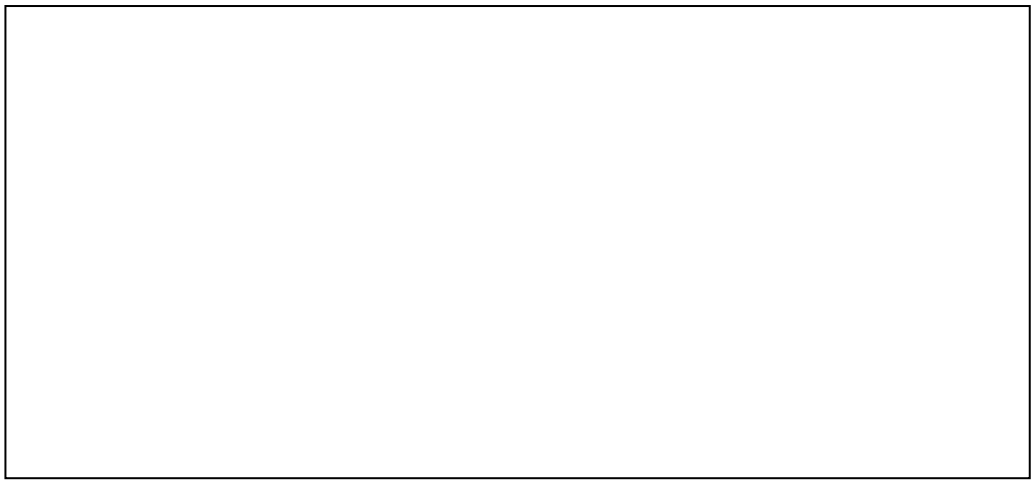
Sample size estimate:

Number of participants randomised:

Number of participants who refused consent:

Numbers analysed for primary outcome variable:

Additional notes/comments:



Appendix 3: Studies excluded from the pilot systematic review described in Chapter 2

Study [ref list at end of appendix]	**Reason for exclusion**
Bellinger 2007 [1]	This study was a secondary analysis of a previously published randomised controlled trial
Berrak 2007 [2]	This trial included participants more than 18 years of age
Boivin 2008 [3]	This trial was pseudo-randomised
Chen 2008 [4]	This trial was non-randomised
Jurg 2006 [5]	This trial was non-randomised
Knott 2007 [6]	This trial was non-randomised
Ladas 2010 [7]	This trial included participants more than 18 years of age
Mamtani 2009 [8]	This was a secondary publication- report of functional outcomes of a previously published randomised controlled trial
Manger 2008 [9]	This was a secondary publication- report of a previously published trial
O'Kearney 2009 [10]	This trial was non-randomised
Powell 2008 [11]	This trial was non-randomised

Reference list of excluded studies

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Appendix 4: Description of studies included in the pilot systematic review (Chapter 2)

Author (Year)	Study details
Akbay et al 2010	This study was a randomised controlled trial evaluating the efficacy of topical tramadol in the control of postoperative pain in children after tonsillectomy
Bojang et al 2010	This study was an open-label randomised trial comparing the safety, tolerability and efficacy of three drug combinations for intermittent preventive treatment of malaria in children
Boots 2010	This study was a randomised controlled trial comparing single to multiple application of lidocaine analgesia in paediatric patients undergoing urethral catheterisation procedures
Diez-Domingo2010	This study was a randomised clinical trial to assess the immunogenicity of a Meningococcal C vaccine booster dose administered to children between the ages of 14-18 months
Okan 2010	This study evaluated the analgesic effects of skin- to- skin contact and breastfeeding in procedural pain in healthy term neonates
Schuttelar 2010	This study was a randomised controlled trial comparing the level of care provided by nurse practitioners as compared to dermatologists to children with eczema
Swadi 2010	This study evaluated the efficacy and tolerability of quetiapine compared with risperidone in the treatment of first onset psychosis among 15 and 18-year old adolescents.
Waling 2010	This study was a randomised open trial to evaluate the effect of group sessions with themes regarding food and physical activity on the energy and micronutrient intake of overweight and obese Swedish children
Zampieri 2010	This study was a prospective, randomised controlled study to evaluate the pre and post- surgery use of Vitamin E in surgical incisions in children
Bassiouny 2009	This study was a randomised controlled trial on parenteral nutrition, oxidative stress and chronic lung disease in preterm infants.
Berrard 2009	This study was a randomised controlled trial evaluating the role of a positioning pillow to improve the lumbar puncture success rate in paediatric haematology-oncology patients
Gelotte 2009	This study was a randomised placebo controlled trial of ibuprofen and pseudoephedrine in the treatment of primary nocturnal enuresis in children
Kadan Lottick 2009	This study was a comparison of neurocognitive functioning in children randomised to dexamethasone or prednisone in the treatment of childhood acute lymphoblastic leukaemia
Morita 2009	This study was a randomised prospective study assessing a novel skin traction method for ultrasound guided internal

	jugular vein catheterisation in infants and neonates weighing less than 5 kg
Haas 2009	This study was a randomised, double blind, placebo controlled study to evaluate the safety and efficacy of risperidone in adolescents with schizophrenia
Parker 2009	This study was a randomised controlled trial to compare postoperative pain in children undergoing tonsillectomy using two different techniques, cold steel dissection and coblator dissection
Turk 2009	This study was a clinical trial evaluating the role of silicone earplugs for very low birth weight newborns in intensive care
Beaumont 2008	This study investigated the effectiveness of a new multicomponent social skills intervention with Asperger Syndrome
Greenberg 2009	This study was a randomised controlled trial comparing oral dexamethasone with oral prednisolone in paediatric asthma exacerbations treated in the Emergency department
Lee 2008	This study was a randomised comparison of end tidal sevoflurane concentration for removal of laryngeal mask airway and laryngeal tube in anaesthetised children
Lynch 2008	This study was a randomised double blind study comparing albumin bolus versus normal saline bolus for treating hypotension in neonates
Patrizi 2008	This study was a double blind, randomised clinical study to evaluate the efficacy and safety of MAS063DP in the management of atopic dermatitis in paediatric patients
Szmuk 2008	This study was a prospective randomised comparison of perilaryngeal airway and laryngeal mask airway in paediatric patients
Channon 2007	This study was a multicentre randomised controlled trial of motivational interviewing in teenagers with diabetes
Dewan 2007	This study was a pilot study to assess the impact of supplementation of curd and leaf protein concentrate on nutritional status and immunity in children with protein energy malnutrition
Gazal 2007	This study was a randomised trial comparing the effectiveness of different oral analgesics for relieving pain and distress in children undergoing dental extraction under general anaesthesia
Lewis 2007	This study was a double blind, dose comparison study of topiramate for prophylaxis of basilar type migraine in children
Lottman 2007	This study was a randomised comparison of oral desmopressin lyophilisate (MELT) and tablet formulations in children and adolescents with primary nocturnal enuresis
Manzoni 2007	This study was a randomised trial of prophylactic fluconazole in preterm neonates
Millar 2007	This study was a randomised placebo controlled trial of the effects of midazolam premedication on children's

	postoperative cognition
Ahonen et al 2006	This study was a randomised placebo controlled trial evaluating the role of rizatriptan in migraine attacks in children
Berens et al 2006	This study was a prospective, randomised, double blind comparison of 5 day versus 10 day enteral methadone wean in opioid dependent patients
Boo 2006	This study was a randomised controlled trial of cling film for the prevention of hypothermia in term infants during phototherapy
Hayden 2007	This study was an open, randomised controlled, prospective study assessing the impact of cranial osteopathy for the relief of infantile colic
Ng 2006	This study was a double blind, randomised, controlled study to assess the effectiveness of a stress dose of hydrocortisone for the treatment of refractory hypertension in preterm infants
Luhmann 2006	This study was a randomised comparison of nitrous oxide plus hematoma block versus ketamine plus midazolam for emergency department forearm fracture reduction in children
Mathai 2006	This study was a comparative study of non-pharmacological methods such as non-nutritive sucking (NNS), rocking, massaging, sucrose, distilled water and expressed breast milk (EBM) to reduce the pain of heelpricks in stable term neonates.
Mulenga 2006	This study was a randomised, double blind, placebo controlled trial to compare the efficacy of atovaquone-proguanil and sulphadoxine- pyrimethamine in the treatment of malarial anaemia in Zambian children
Galli 2006	This study was a double blind, randomised placebo controlled trial to perform the safety and effectiveness of double-dose intradermal β-Glucuronidase therapy in preventing chronic rhinoconjunctivitis and/or asthma in children

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Appendix 5: Summary of missing and unclear information in trial reports and contact with authors

Trial report	Missing information	Unclear information	Authors' responses
2010			
Akbay	numbers refusing consent, numbers included in analysis of primary outcome		no response
Bojang	numbers refusing consent	numbers randomised, numbers included in analysis of primary outcome	Author wanted the query to be sent formally to their ethics committee for review and decision.
Boots	numbers refusing consent		did not record
Diez-Domingo	numbers refusing consent		did not record
Zampieri	numbers refusing consent, sample size estimate		no response
Swadi	sample size estimate		no response
2009			
Bassiouny	sample size estimate		sample of convenience
Gelotte	numbers refusing consent		did not record data on consent refusal, no response about sample size estimate
Kadan-Lottick	sample size estimate		no response
Morita	numbers refusing consent		no consent refusal
Turk	numbers refusing consent, sample size estimate		did not record consent refusals sample size of convenience
2008			
Beaumont	numbers refusing consent, sample size estimate, numbers included in analysis of primary outcome		no response
Greenberg	numbers refusing consent	numbers included in analysis of primary outcome	no response
Lee	numbers refusing consent, sample size estimate		no response
Lynch	numbers refusing consent	numbers randomised, numbers included in analysis of primary outcome	no response
Patrizi	numbers refusing consent, sample size		3 refused consent, no sample size

	estimate		calculation
Szmuk	numbers refusing consent		did not record information, estimate 10-15%
2007			
Dewan	numbers refusing consent, sample size calculation		consent rate not recorded, estimate 15%; no sample size calculation-pilot study
Ghazal	numbers refusing consent		6 refused consent
Lewis	numbers refusing consent, sample size estimate		no response
Lottman	numbers refusing consent		don't have information
Manzoni	sample size estimate		no response
Millar	numbers refusing consent		no response
2006			
Ahonen	numbers refusing consent		no response
Berens	numbers refusing consent, sample size estimate		no response
Hayden	numbers refusing consent, sample size estimate		no response
Luhman	numbers refusing consent		no response
Mathai	numbers refusing consent, sample size estimate, numbers included in analysis of primary outcome		no response
Mulenga	numbers refusing consent		no response
Galli	numbers refusing consent, sample size estimate		no response

Appendix 6: Correspondence with NIHR CRN coordinating centre, 15/11/2010

From: Kaur, Geetinder [mailto:Geetinder.Kaur@liverpool.ac.uk]
Sent: 15 November 2010 23:51
To: Joanna Olliver
Cc: Smyth, Rosalind; Williamson, Paula
Subject: Request for information

Dear Dr Olliver,

My name is Dr Geetinder Kaur and I'm a clinical PhD student (MRC funded) in the MRC North West Hub for Trials Methodology Research and Department of Women's and Children's Health at the University of Liverpool under the supervision of Professor Rosalind Smyth (Director of NIHR Medicines for Children Research Network and Director of Clinical Research at University of Liverpool) and Professor Paula Williamson (Associate Director, NIHR MCRN and Director of the MCRN Clinical Trials Unit).

The aim of our research is to review the recruitment and retention of children in clinical trials to assess the magnitude of the problem and identify the factors which influence the same. We are interested in this area because under-recruitment and attrition are known to be common problems and have an adverse effect on the success of a clinical trial; however there is limited research on the subject in children. There is a need to study the subject further in children in a holistic manner so that effective strategies can be developed to counter these problems.

We would like to review the trials in children in the NIHR portfolio, and compare them to trials in adults in the NIHR portfolio. I would like to enquire if it is possible to gain access to the NIHR portfolio database (with appropriate confidentiality safeguards) for trials in the MCRN portfolio and other networks. If so, I would be grateful if you could outline the procedure to seek permission to do this. We can supply a protocol for our planned research.

Many Thanks

Kind Regards
Dr Geetinder Kaur
Clinical Research Fellow
Institute of Child Health
Alder Hey Hospital
Liverpool

From: Joanna Olliver [joanna.r.olliver@nihr.ac.uk]
Sent: 23 November 2010 21:58
To: Kaur, Geetinder
Subject: RE: Request for information

Dear Geetinder,

I am looking into this for you and will be in touch ASAP with further information regarding whether access could be granted and if so what the permissions process would be.

Kind regards
Joanna
Dr Joanna Olliver
Acting Portfolio Lead

NIHR CRN CC
T: 0113 343 0374
E: joanna.r.olliver@nihr.ac.uk

Response received 10/12/2010

RE: Request for information
From: Joanna Olliver joanna.r.olliver@nihr.ac.uk
Sent: 10 December 2010 10:40
To: Kaur, Geetinder <gkaur@liverpool.ac.uk>
Cc: Williamson, Paula <prw@liverpool.ac.uk>

Dear Geetinder,

I have discussed this with colleagues in the NIHR Clinical Research Network Coordinating Centre and unfortunately we are unable to give you the access to the Portfolio Database that you have requested. Current access for NHS Trusts or Universities is via the public search tool or reporting. It may be that the data you require could be made available via a reporting request and would advise you initially to make this request to the MCRN Coordinating Centre. If the Portfolio Managers in the MCRN Coordinating Centre do not have the appropriate permissions to be able to provide you with the report you require, please do get back in touch as this may be something that the NIHR CRN Coordinating Centre Information Management Team could provide you with.

Best of luck with your research project

Kind regards
Joanna

Appendix 7: Format of existing data and modifications for use in NIHR portfolio review (Chapter 3)

The study lists and recruitment data requested from the NIHR CRN coordinating centre was provided in excel spread-sheets. 'Meds Children' (MCRN studies) were selected from the 'Topic Study Summary' report May 2013. The data was present under the following headings:

- Main Topic / Portfolio study ID / IRAS project ID / Study acronym/short title / Study title
- Active status: Open/closed-in follow up, closed-follow up complete, suspended
- Portfolio eligibility: adopted commercial study, adopted non-commercial study, automatically eligible
- Commercial study?: commercial/non-commercial
- Main Network (supporting network) / NIHR owning organisation
- Lead country: England/Wales/Northern Ireland/Scotland/ unknown/non-UK country/null
- All Topics: Main Topic (Supporting Topics)
- Primary CSG/ All CSG/Main topic disease
- Randomisation
- Study design/ intervention type/observational type
- Phase/study setting/geographical scope
- Actual/planned original opening and closing dates
- Global sample size/UK sample size
- CI name and details
- Funder/sponsor
- ISRCTN/MREC number
- Study notes

The excel spread-sheet was filtered to identify studies with:

- Main or supporting network being 'Medicines for Children'
- Randomisation status: randomised and both. The randomisation status of studies labelled 'both' was confirmed by checking the study protocols.
- Active status: closed –in follow up and follow up complete
- Study duration-April 2006 and beyond up to March 2013.

For the Paediatric non-medicinal studies, the report were filtered to identify studies under 'Generic Relevance and Cross cutting themes'. Filters for randomisation status, active status (closed in follow up and follow up complete) and study duration were applied similar to MCRN studies described previously. The required data was transferred to an excel spread-sheet for purposes of the current study. The identified studies were listed with Study ID, randomisation status that was confirmed with study teams/protocol, active status, geographical scope (international, UK single or multicentre), commercial/publicly funded, information on original and actual opening and closing dates, original sample sizes and actual recruitment.

Information on factors affecting recruitment was obtained from NIHR CRN and studies were classified as IMP/non-IMP based on type of intervention, and acute/chronic/healthy based on type of disease. The CIs and study teams were sent an online questionnaire to gather information about pilot/feasibility assessment, CTU involvement, trial management and additional trial demands.

Appendix 8: Recruitment discrepancies and recruitment information from various sources for UK based studies in NIHR portfolio review (Chapter 3)

MCRN trials
Sources of data

Name of Trial		NIHR report
Target sample size		NIHR reports: original and planned sample size, CI questionnaire, protocol
UK recruitment		NIHR reports: UK recruitment, CI questionnaire, ClinicalTrials.gov (International studies)
Target recruitment period (months)		NIHR reports: original closure date - original opening date (days); divided by 30 for number of months, CI questionnaire, SAC form
Actual recruitment period (months)		NIHR report: actual closure date - actual opening date (days); divided by 30 for number of months
Recruitment success (P)		S if recruited to 100% or more of original recruitment target
Recruitment success (S)		S if recruited to 100% target or more in a period not exceeding 10% of originally planned recruitment period
Target revised		Questionnaire sent to CI
Recruitment discontinued earlier than planned		Questionnaire sent to CI
Extension requested		Questionnaire sent to CI
Extension granted		Questionnaire sent to CI
Notes		Additional information from MCRN files and correspondence with CIs/study teams (if applicable)
Discrepancy		
Action rule		

ADEPT

Target sample size	400	Original sample size 400 as per CI and NIHR report, planned sample size 400
UK recruitment	404	as per CI and NIHR data
Target recruitment period (months)	24	28 as per original opening and closing dates in NIHR report but 24 months in protocol, 24 as per CI
Actual recruitment period (months)	39	39 months
Recruitment success (P)	S	Recruited to 100% target
Recruitment success (S)	U	Recruited to 100% target in a period exceeding 10% beyond the planned recruitment period
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	Y	Both (cost and time extension); recruitment slower than anticipated
Extension granted	Y	
Discrepancy		Target recruitment period
Action rule	1	Figure provided by CI matches the figure in protocol

Amitriptyline in EB Pain

Target sample size	40	Original sample size 40 as per NIHR report but 30 as per CI, planned sample size 40, 40 in protocol
UK recruitment	31	31 as per NIHR data but 22 as per CI

Target recruitment period (months)		24 as per original opening and closing dates in NIHR report but 12 months as per CI
Actual recruitment period (months)	41	
Recruitment success (P)	U	failed to recruit to 100%
Recruitment success (S)	U	failed to recruit to 100% target
Target revised	N	
Recruitment discontinued earlier than planned	N	No
Extension requested	Y	No cost extension (time only); Delay in receiving placebo IMP, slow recruitment
Extension granted	Y	had a no cost extension
Discrepancy		Target recruitment period and numbers recruited
Action rule	1	NIHR figure for target recruitment period accepted as matches with protocol, corresponding NIHR figure for recruitment numbers accepted. Outcome same with either NIHR or CI data

An alternative booster vaccine against meningitis and ear infections

Target sample size	168	Original sample size 168 as per NIHR report but 178 as per CI, planned sample size 168, 168 in protocol
UK recruitment	178	178 as per NIHR data and CI
Target recruitment period (months)	7	7 as per original opening and closing dates in NIHR report and CI
Actual recruitment period (months)	5	
Recruitment success (P)	S	Recruited to 100% target
Recruitment success (S)	S	Recruited to 100% target in a period not exceeding 10% beyond the planned recruitment period
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	N	
Discrepancy		Target sample size
Action rule	1	NIHR figure for target sample size accepted as matches with protocol

BOOST II UK

Target sample size	1200	Original sample size 1200 as per NIHR report and CI, planned sample size 1200, 1200 in protocol
UK recruitment	973	973 as per NIHR data and CI
Target recruitment period (months)	48	91 as per original opening and closing dates in NIHR report but 49 months as per intended opening and closing dates in SAC form, 48 months as per CI
Actual recruitment period (months)	39	
Recruitment success (P)	S	
Recruitment success (S)	S	
Target revised	N	
Recruitment discontinued earlier than planned	Y	As per CI- Data monitoring committee (DMC) recommended to the Trial steering committee that recruitment should cease because a meta-analysis of the on-going trials showed a highly significant and

		unexpected difference in mortality
Extension requested	N	
Discrepancy		Target recruitment period
Action rule	1	CI figure for target recruitment period accepted as close to figure as per SAC form
Query and rationale		Numbers recruited to the trial less than the planned target but trial recruitment discontinued early due to difference in mortality. The numbers recruited just exceed the recruitment target for the duration of recruitment to the trial.

Bronchiolitis of Infancy Discharge Study (BIDS)

Target sample size	600	Original sample size 720 as per NIHR report but 600 as per CI, planned sample size 600, 600 in protocol
UK recruitment	615	615 as per NIHR data and CI
Target recruitment period (months)	12	24 months as per original opening and closing dates in NIHR report, 24 months as per SAC form, 12 months as per CI
Actual recruitment period (months)	12	18 months as per NIHR data but 12 months as per CI
Recruitment success (P)	S	recruited to 100% target
Recruitment success (S)	S	Recruited to 100% target in a period not exceeding 10% beyond the planned recruitment period
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	N	
Discrepancies		Target sample size- planned sample size accepted as target as matches with figure in protocol and that provided by CI. Target and actual recruitment period- Discrepancies clarified by CI
Notes		As per CI questionnaire: Recruitment was planned as 2 x 6 month winter bronchiolitis seasons. CI has confirmed that the trial recruited precisely to schedule a per protocol and agreement signed with NIHR
Action rule	1 2	Target sample size Target recruitment period

CATCH

Target sample size	1200	Original sample size 1200 as per NIHR report and CI
UK recruitment	1484	1484 as per NIHR data and 1450 as per CI, 1484 as per trial coordinator at CTU
Target recruitment period (months)	20	37 months as per original opening and closing dates in NIHR report, 24 months as per CI, 36 months as per SAC form. 20 months as per dates provided by trial coordinator.
Actual recruitment period (months)	23	25 months as per NIHR report, 23 months as per dates provided by trial coordinator
Recruitment success (P)	S	Recruited to 100% target
Recruitment success (S)	U	Recruited to 100% target in a period exceeding 10% beyond the planned recruitment period

Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	Y	No cost extension requested to ensure data capture and because centres started late.
Extension granted	Y	
Notes		Recruitment dates provided by the trial coordinator Planned recruitment period: June 2010 – 31 Jan 2012 (dates given to the HTA in the milestones). Actual recruitment period: 1 Oct 2010 – 31 August 2012 (dates given by Stats team recruitment graph), no cost extension recruitment extended to 28 Feb 2013
Discrepancy		Numbers recruited and target recruitment period
Action rule	2	Information obtained from the trial coordinator

CHIP trial

Target sample size	1500	Original sample size 1500 as per NIHR report and CI
UK recruitment	1384	1384 as per NIHR data and 1372 as per CI, 1384 on website
Target recruitment period (months)	24	24 months as per original opening and closing dates in NIHR report, CI has not provided the data, 24 months in protocol
Actual recruitment period (months)	41	
Recruitment success (P)	U	Did not recruit to 100% target
Recruitment success (S)	U	
Revision of target	N	
Recruitment discontinued earlier than planned	N	
Extension requested	Y	
Extension granted	Y	Limited extension granted with modified follow-up (no follow-up at 1 year for final 12 months of recruitment)
Discrepancy		Numbers recruited and target recruitment period
Action rule	1	Numbers recruited- NIHR figure matches with the figure on study website Target recruitment period- NIHR data matches protocol

Cognative GA Study - TIVA versus volatile anaesthesia in children: cognitive effects

Target sample size	150	Original sample size 150 as per NIHR report and 80 as per CI
UK recruitment	58	0 as per NIHR data and 32 as per CI
Target recruitment period (months)	36	4 months as per original opening and closing dates in NIHR report, 36 months as per CI
Actual recruitment period (months)	41	41 months as per NIHR report
Recruitment success (P)	U	
Recruitment success (S)	U	
Target revised	Y	One revision. recruitment to the trial was very effective but repeated staff shortages and cancellation of clinics meant that many patients who had consented to participate were lost to the study

Recruitment discontinued earlier than planned	N	
Extension requested	Y	No cost extension - To increase the sample size to a satisfactory number for statistical purposes
Extension granted	Y	
Discrepancy		Target sample size, numbers recruited and target recruitment period
Action rule	2	The CI confirmed that the original intention was to recruit 150 patients and the target was revised down to 80. The study was originally planned to run over 36 months and 58 patients were randomised in the study. The original recruitment target was accepted as it was brought down due to problems with recruitment and there was insufficient information to justify reduction in sample size.

DECIDE

Target sample size	200	Original sample size 240 as per NIHR report and CI, planned sample size 200
UK recruitment	203	203 as per NIHR data and CI
Target recruitment period (months)	18	18 months as per original opening and closing dates in NIHR report and CI
Actual recruitment period (months)	40	40 months as per NIHR report
Recruitment success (P)	S	Recruited to 100% target
Recruitment success (S)	U	Recruited to 100% target in a period exceeding 10% beyond the planned recruitment period
Target revised	Y	Revised once downwards to 200 in the context of trial progress and experience of drop-outs.
Recruitment discontinued earlier than planned	N	
Extension requested	Y	No cost extension- Slower than anticipated recruitment rates.
Notes (MCRN files)		The original sample size was calculated at 200 but set at 240 to allow for a 17% withdrawal rate, however the withdrawal rate has been minimal (only 1 patient). Recruitment was slower than anticipated throughout the trial and so the decision was made by the TSC (acting as IDMC) in conjunction with the TMG, to cease recruiting on 31st October 2011 when it was calculated that 200 patients would have been recruited. In fact by this date 203 patients were recruited.
Action rule	1	The planned sample size of 200 was accepted as target sample size since the original target was revised due to a reduced drop-out rate. This information was obtained from MCRN study records.

DRN067 (FACTS)

Target sample size	300	Original sample size 300 as per NIHR report and CI
UK recruitment	305	305 as per NIHR data and CI
Target recruitment period	12 or 18	12 months as per original opening and closing dates

(months)		in NIHR report, 18 months as per CI
Actual recruitment period (months)	24	24 months as per NIHR report
Recruitment success (P)	S	Recruited to 100% target
Recruitment success (S)	U	Recruited to 100% target in a period exceeding 10% beyond the planned recruitment period
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	Y	No cost extension
Extension granted	Y	
Reason for requesting extension		It was expected that all sites would recruit simultaneously but delays in local R&D approvals as well as staff health issues (20 paediatric nurses/dietetians having babies, maternity leave, sick leave etc)and NHS structural changes (some sites were completely relocated from NHS site into community during the trial)all contributed to staggered recruitment.
Discrepancy		Target recruitment period
Action rule	1	Outcome same with NIHR data and information provided by CI

H1N1

Target sample size	1000	Original sample size 1000 as per NIHR report, and CI
UK recruitment	943	943 as per NIHR data and CI
Target recruitment period (months)	2	3 months as per NIHR report, 2 months as per CI
Actual recruitment period (months)	1	1 month
Recruitment success (P)	S	
Recruitment success (S)	S	
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	N	
Notes		Numbers recruited to the trial less than the planned target but recruitment to the study took place over 5 weekends and study stopped at 943 because data was needed ASAP due to the nature of the study. The numbers recruited exceed the recruitment target for the actual duration of recruitment to the study.

I2S2

Target sample size	1100-1700	Original sample size 650 as per NIHR report, 1300 as per CI, 110-1700 in protocol, planned sample size 1400
UK recruitment	1275	1275 as per NIHR data and CI
Target recruitment period (months)	27	41 months as per NIHR report, 36 months as per CI
Actual recruitment period (months)	33	34 month

Recruitment success (P)	S	recruited to 100% target
Recruitment success (S)	U	recruited to 100% target
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	Y	Both cost and time extension because of slower than anticipated recruitment
Extension granted	Y	
Discrepancy		Target sample size and target recruitment period
Action rule	2	CI confirmed that target recruitment period was 27 months and actual recruitment period was 33 months; the target recruitment was a range from 1100 to 1700; 1400 was arbitrarily selected as a range could not be entered.

INDIGO - Pump versus MDI insulin and hypoglycaemia in children.

Target sample size	10	Original sample size 10 as per NIHR report
UK recruitment	10	10 as per NIHR data , 10 as per study report sent by CI
Target recruitment period (months)	24	24 months as per NIHR report
Actual recruitment period (months)	32	32 months
Recruitment success (P)	S	recruited to 100% target
Recruitment success (S)	U	recruited to 100% target in a period exceeding 10% of planned recruitment period
Target revised		Information not available
Recruitment discontinued earlier than planned		Information not available
Extension requested		Information not available
Notes		CI did not respond to the questionnaire

MAGNETIC

Target sample size	500	Original sample size 500 as per NIHR report and CI, planned sample size 20
UK recruitment	508	508 as per NIHR data and CI
Target recruitment period (months)	24	24 months as per NIHR report, 24 months as per trial coordinator
Actual recruitment period (months)	28	28 months
Recruitment success (P)	S	recruited to 100% target
Recruitment success (S)	U	Recruited to 100% target in a period exceeding 10% of planned recruitment period
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	N	
Notes		

MASCOT

Target sample size	450	Original sample size 450 as per NIHR report and 900 as per CI, planned sample size 450. Checked MCRN files- target for registration 900 and randomisation 450
UK recruitment	160	170 as per NIHR data and 160 as per CI
Target recruitment period (months)		12 months as per NIHR report, 24 months as per CI
Actual recruitment period (months)		18 months
Recruitment success (P)	U	Did not recruit to 100% target
Recruitment success (S)	U	Did not recruit to 100% target
Target revised	N	
Recruitment discontinued earlier than planned	Y	Funders unwilling to continue
Extension requested	Y	Both cost and time- not granted
Extension granted	N	
Discrepancy		Target sample size
Action rule	1	

MCRN 002

Target sample size	600	Original sample size 250 as per NIHR report, 600 as per CI, planned sample size 250. 600 in protocol
UK recruitment	278	146 as per NIHR data and 286 as per CI
Target recruitment period (months)	3	19 months as per NIHR report and 3 months as per CI
Actual recruitment period (months)	8	8 months
Recruitment success (P)	U	
Recruitment success (S)	U	
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	N	
Discrepancy		Target sample size, numbers recruited and target recruitment period
Action rule	1 2	Target sample size- figure provided by CI matches the figure in protocol Numbers recruited and target recruitment period clarified with the study team

MCRN 033

Target sample size	280	Original sample size 280 as per NIHR report and CI, planned sample size 280, 280 in protocol
UK recruitment	280	284 as per NIHR data, 280 as per CI
Target recruitment period (months)	5	14 months as per NIHR report and 5 months as per CI
Actual recruitment period (months)	6	6 months (165 days)
Recruitment success (P)	S	recruited to 100% target

Recruitment success (S)	S	Recruited to 100% target in a period not exceeding 10% of planned recruitment period
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	N	
Discrepancy		Target recruitment period
Action rule	1	

MCRN 089

Target sample size	384	Original sample size 300 as per NIHR report, 384 as per CI, planned sample size 384, 384 in protocol
UK recruitment	385	385 as per NIHR data, 384 as per CI
Target recruitment period (months)	15	15 months as per NIHR report, 12 months as per CI
Actual recruitment period (months)	11	11 month
Recruitment success (P)	S	recruited to 100%
Recruitment success (S)	S	Recruited to 100% target in period not exceeding 10% of planned recruitment period
Target revised	N	
Recruitment discontinued earlier than planned	Y	Recruitment target reached early
Extension requested	N	
Notes		Target sample size 384 and numbers recruited 385 as per MCRN study files
Discrepancy		Target sample size and numbers recruited
Action rule	1	

MCRN 164

Target sample size	284	Original sample size 284 as per NIHR report, 284 as per CI, planned sample size 284, 284 in protocol
UK recruitment	284	284 as per NIHR data, 284 as per CI
Target recruitment period (months)	6	5 months as per NIHR report, 6 months as per CI, 6 months as per SAC form
Actual recruitment period (months)	7	7 months (219 days)
Recruitment success (P)	S	Recruited to 100% target
Recruitment success (S)	U	Recruited to 100% target in a period exceeding 10% of planned recruitment period
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	N	
Notes		

MENDS

Target sample size	172	Original sample size 172 as per NIHR report, 180 as per CI, planned sample size 172, 172 in protocol
UK recruitment	146	146 as per NIHR data, 180 as per CI, 146 as per CTU
Target recruitment period (months)	9	9 months as per NIHR report, CI not stated
Actual recruitment period	32	32 months

(months)		
Recruitment success (P)	U	Did not recruit to 100% target
Recruitment success (S)	U	Did not recruit to 100% target
Target revised	Y	
Recruitment discontinued earlier than planned	N	
Extension requested	Y	Both time and cost extension requested. Slow early recruitment rate (many reasons for this): time extension. Add-on genetic study which required funding: cost (money) extension
Extension granted	Y	
Discrepancy		Target sample size and numbers recruited
Action rule	1	Information requested from the Clinical Trials Unit

MIGS

Target sample size	60	Original sample size 60 as per NIHR report, 60 as per CI, planned sample size 60, 60 in protocol
UK recruitment	62	62 as per NIHR data, 62 as per CI
Target recruitment period (months)	33	16 months as per NIHR report, 33 months as per CI
Actual recruitment period (months)	32	32 months
Recruitment success (P)	S	recruited to 100% target
Recruitment success (S)	S	Recruited to 100% target in a period not exceeding 10% of planned recruitment period
Target revised	Y	CI questionnaire- 2 patients replaced due to not meeting timing of primary endpoint, discussed at DMEC and ratified by TSC
Recruitment discontinued earlier than planned	N	
Extension requested	N	
Discrepancy		Target recruitment period
Action rule	1	

Nephrotic Syndrome

Target sample size	50	Original sample size 50 as per NIHR report, 50 as per CI, planned sample size 50, 50 in protocol
UK recruitment	53	53 as per NIHR data, 53 as per CI
Target recruitment period (months)	24	35 months as per NIHR data, 24 months as per CI
Actual recruitment period (months)	20	20 months
Recruitment success (P)	S	Recruited to 100% target
Recruitment success (S)	S	Recruited to 100% target in planned recruitment period
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	N	
Discrepancy		Target recruitment period
Action rule	1	

NEST

Target sample size	118	Original sample size 118 as per NIHR report, 94 as per CI, planned sample size 118, 118 in protocol
UK recruitment	111	111 as per NIHR data, 96 as per CI
Target recruitment period (months)	35	35 months as per NIHR data, 36 months as per CI
Actual recruitment period (months)	46	46 months
Recruitment success (P)	U	
Recruitment success (S)	U	
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	Y	Both time and cost extension.
Extension granted	Y	H1N1 epidemic prevented availability of ECMO beds in UK
Discrepancy		Target sample size and numbers recruited
Action rule	1	Information checked on study website: target 118, numbers recruited 111

P3MC

Target sample size	600	Original sample size 600 as per NIHR report, 600 as per CI, planned sample size 600
UK recruitment	47	47 as per NIHR data, 47 as per CI
Target recruitment period (months)	24	43 months as per NIHR data, 24 months as per CI
Actual recruitment period (months)	12	12 months
Recruitment success (P)	U	Did not recruit to 100% target
Recruitment success (S)	U	Did not recruit to 100% target
Target revised	N	
Recruitment discontinued earlier than planned	Y	
Extension requested	N	
Notes		The funding was pulled due to poor recruitment rates. This was recommended by the Trial Steering Committee and agreed by the funders.

POP study

Target sample size	216	Original sample size 270 as per NIHR report, 270 as per CI, planned sample size 216
UK recruitment	217	210 as per NIHR data, 217 as per CI
Target recruitment period (months)	18	31 months as per NIHR data, 18 months as per CI
Actual recruitment period (months)	52	52 months
Recruitment success (P)	S	
Recruitment success (S)	U	
Target revised	Y	
Recruitment discontinued earlier than planned	N	
Extension	Y	
Notes (CI questionnaire)		One revision. The sample size was calculated initially at 270. Using an increase of 0.5 SDS in

		BMD in the treated group compared to the control for a test with 80% confidence and a significance level of 5%, we will require 75 children in each of the three study arms, (225) allowing for a 15% dropout rate. It was further expected that approximately 20% of this population will not receive steroids for 3 months. Thus to ensure that an adequate number of children do complete the study on steroids we had planned to recruit 90 children to each arm; a total of 270. However at the interim analysis the dropout rate was much lower than anticipated and the majority of children received steroids for more than 3 months. The trial statistician reanalysed the power calculation Sample size required: 216
Discrepancy		Target sample size, numbers recruited
Action		216 accepted as target sample size as reduction in sample size due to reduced drop-out rate

Salford Bright Smiles Baby Study

Target sample size	660	Original sample size 732 as per NIHR report, 660 as per CI, planned sample size 330, 732 in protocol
UK recruitment	409	330 as per NIHR data, 409 as per CI
Target recruitment period (months)	6	6 months as per NIHR data and CI
Actual recruitment period (months)	14	14 months
Recruitment success (P)	U	
Recruitment success (S)	U	Did not recruit to 100% target
Target revised	Y	
Recruitment discontinued earlier than planned	N	
Extension	Y	No cost, underestimation of recruitment period
Notes (CI questionnaire)		Target reduced from 660 to 330 as new evidence available to support reduced sample size (would still be able to determine effect). Re-opened recruitment due to underestimation of drop out, to increase sample size to current 409.
Notes (MCRN files)		A comprehensive review of the study has been undertaken due to concerns that the original sample size (n =630) would not be achieved within a reasonable time frame. Part of the review re-examined the setting of the minimum clinically significant difference. At the time of writing the original bid, the Cochrane Review of the efficacy of fluoride varnishes informed this decision (1). A re-examination of this Cochrane Review identified that it had been published in 2002 and not updated. Further, that no studies involved the very young age group of our trial were included. A more recent study (Weintraub et al, 2006) (2) has been conducted to GCP in early childhood caries. This trial of fluoride varnish in children of a similar age group showed an odds ratio of 3.5 in caries incidence for children randomised to receive 2 fluoride varnish applications per year. This new information

		informed a fresh discussion of the minimum clinically significant difference and led to the decision that this be reduced from 20% with caries in the test groups to 17.5% with caries. Therefore the revised sample size will be 330 participants and we have so far accrued 60 % of this new final target
Discrepancy		Target sample size and numbers recruited
Action rule	1	target sample size accepted as 660 because target revised down due to recruitment difficulties

SCAMP

Target sample size	150	Original sample size 150 as per NIHR report, planned sample size 150, 150 in protocol
UK recruitment	115	115 as per NIHR data
Target recruitment period (months)	24	24 months as per NIHR data
Actual recruitment period (months)	34	34 months
Recruitment success (P)	U	Did not recruit to 100% target
Recruitment success (S)	U	Did not recruit to 100% target
Target revised		Information not available
Recruitment discontinued earlier than planned		Information not available
Extension		Information not available

StePS

Target sample size	90	Original sample size 90 as per NIHR report, 90 as per CI, planned sample size 90
UK recruitment	29	29 as per NIHR data and CI
Target recruitment period (months)	24	18 months as per NIHR data, 24 months as per CI
Actual recruitment period (months)	51	51 months
Recruitment success (P)	U	Did not recruit to 100% target
Recruitment success (S)	U	Did not recruit to 100% target
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	Y	No cost extension
Extension granted	Y	Requested for low recruitment
Discrepancy		Target recruitment period
Action rule	1	

SWET

Target sample size	310	Original sample size 310 as per NIHR report, 310 as per CI, planned sample size 336, 310 in protocol
UK recruitment	336	440 as per NIHR data and 336 as per CI
Target recruitment period (months)	18	18 months as per NIHR data, not mentioned by CI, 18-20 months in protocol
Actual recruitment period (months)	26	26 months
Recruitment success (P)	S	recruited to 100% target

Recruitment success (S)	U	recruited to 100% target in a period exceeding 10% of the planned recruitment period
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	N	
Discrepancy		Numbers recruited
Notes		Numbers recruited, target and actual recruitment period checked on study website and publication

The first BCVC nasal flu vaccine study

Target sample size	151	Original sample size 200 as per NIHR report, 200 as per CI, planned sample size 151, 200 in protocol
UK recruitment	152	151 as per NIHR data and 152 as per CI
Target recruitment period (months)	2	4 months as per NIHR data, 2 months as per CI
Actual recruitment period (months)	2	2 months
Recruitment success (P)	S	Recruited to 100% target
Recruitment success (S)	S	Recruited to 100% target in a period not exceeding 10% of planned recruitment period
Target revised	Y	one revision original sample size arbitrary as no data available to estimate likely size of effect the relevance of which is biological rather than clinical
Recruitment discontinued earlier than planned	N	
Extension		
Notes (MCRN files)		The 200 target was pretty arbitrary - roughly what we thought we would be able to get in the time available. The aim of the study is to see if there is any biological effect of vaccination on bacterial carriage. 152 will permit us to do that.
Discrepancy		Target sample size
Action		151 accepted as target sample size

TIPIT

Target sample size	150	Original sample size 150 as per NIHR report, 150 as per CI, planned sample size 150, 150 in protocol
UK recruitment	153	153 as per NIHR data and 153 as per CI
Target recruitment period (months)	24	27 months as per NIHR data, 24 as per CI
Actual recruitment period (months)	19	19 months
Recruitment success (P)	S	Recruited to 100% target
Recruitment success (S)	S	Recruited to 100% target in a period not exceeding 10% of planned recruitment period
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	N	
Discrepancy		Target recruitment period
Action rule	1	

Treatments for Childhood Crohn's Disease

Target sample size	80	Original sample size 80 as per NIHR report, 80 as per CI, planned sample size 80, 80 in protocol
UK recruitment	83	84 as per NIHR data and 83 as per CI
Target recruitment period (months)	24	16 months as per NIHR data, 24 as per CI
Actual recruitment period (months)	16	16 months
Recruitment success (P)	S	Recruited to 100% target
Recruitment success (S)	S	Recruited to 100% target in a period not exceeding 10% of planned recruitment period
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	N	
Discrepancy		Target recruitment period
Action rule	1	

Wheeze and Intermittent Treatment: WAIT

Target sample size	1300	Original sample size 1300 as per NIHR report, 1300 as per CI, planned sample size 1300
UK recruitment	1368	1368 as per NIHR data and 1367 as per CI
Target recruitment period (months)	24	24 months as per NIHR data, 24 as per CI
Actual recruitment period (months)	26	26 months
Recruitment success (P)	S	Recruited to 100% target
Recruitment success (S)	S	Recruited to 100% target in a period not exceeding 10% of planned recruitment period
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	Y	
Extension granted	Y	
Notes		A 6 month funding and 18 month time extension was requested. This represented 6 months additional active recruiting time and 12 months to account for a delay in starting recruitment. In effect only one extra month of recruitment was required but the additional data analysis time and closing out time was invaluable.

Paediatric Non-medicines studies

A Pilot Study to Explore the Feasibility of Computerised CBT for Children

Target sample size	45	Original sample size 45 as per CI and NIHR report
UK recruitment	20	19 as per NIHR data and 20 as per CI
Target recruitment period (months)	12	12 as per original opening and closing dates in NIHR report and CI
Actual recruitment period (months)	13	13 months
Recruitment success (P)	U	Did not recruit to 100% target

Recruitment success (S)	U	Did not recruit to 100% target
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	N	

AIRS

Target sample size	295	Original sample size 294 as per NIHR report and 295 as per CI
UK recruitment	320	341 randomisation events as per NIHR data and 320 as per CI
Target recruitment period (months)	24	8 months as per original opening and closing dates in NIHR report and 24 months as per CI
Actual recruitment period (months)	36	36 months
Recruitment success (P)	S	Recruited to 100% target
Recruitment success (S)	U	Recruited to 100% target in a period exceeding 10% of the planned recruitment period
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension	N	
Discrepancy		Numbers recruited
Action rule	1	

Atomoxetine HSEN

Target sample size	40	Original sample size 40 as per NIHR report and CI
UK recruitment	15	11 as per NIHR data and 15 as per CI
Target recruitment period (months)	36	17 months as per original opening and closing dates in NIHR report and 36 months as per CI
Actual recruitment period (months)	22	22 months
Recruitment success (P)	U	Did not recruit to 100% target
Recruitment success (S)	U	Did not recruit to 100% target
Target revised	N	
Recruitment discontinued earlier than planned	Y	insufficient recruitment
Extension requested	N	
Discrepancy		Numbers recruited and target recruitment period
Action rule	1	

Baby wipes trial

Target sample size	280	Original sample size 280 as per NIHR report and CI
UK recruitment	280	280 as per NIHR data and CI
Target recruitment period (months)	9	12 months as per original opening and closing dates in NIHR report and 9 months as per CI
Actual recruitment period (months)	9	13 months as per NIHR data, 9 months as per study team and publication
Recruitment success (P)	S	Did not recruit to 100% target
Recruitment success (S)	S	
Target revised	Y	Initial recruitment target based on available thigh data. One planned revision, agreed by Data Monitoring Committee, based on data collected at buttocks on first 29 participants. Sample size reduced to at least 266 (133 participants per group).

Recruitment discontinued earlier than planned	N	
Extension requested	N	
Discrepancy		Target recruitment period and actual recruitment period
Action rule	1	Information checked with study statistician and in published report

CHAFFINCH Trial Pilot

Target sample size	32	Original sample size 40 as per NIHR report and CI
UK recruitment	32	29 as per NIHR data and 32 as per CI
Target recruitment period (months)	3	2 months as per original opening and closing dates in NIHR report and 3 months as per CI
Actual recruitment period (months)	5	5 months
Recruitment success (P)	S	Did not recruit to 100% target
Recruitment success (S)	U	Did not recruit to 100% target
Target revised	Y	For the pilot study, we initially planned to recruit 40 children. In line with the CLRN guidelines, when we observed that there would be enough children for the pilot, we reduced the target to 80% i.e. 32 children
Recruitment discontinued earlier than planned	N	
Extension requested	Y	No cost extension
Extension granted	Y	Preparation of the material related to good clinical practice (GCP) and to homogenise forms between the College and the participant Trusts.
Action		Revised target of 32 accepted

CLICK-EAST: The Edinburgh Autism Social-attention Trial

Target sample size	60	Original sample size 60 as per NIHR report and CI
UK recruitment	61	61 as per NIHR data and 54 as per CI
Target recruitment period (months)	18	18 months as per original opening and closing dates in NIHR report and CI
Actual recruitment period (months)	9	9 months
Recruitment success (P)	S	
Recruitment success (S)	S	
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	N	
Notes (Information requested from CI)		61 children were assessed at baseline and their parents gave consent. 54 children began the trial. There were seven children who did not meet inclusion criteria so they were recruited but not enrolled. Recruitment was 9 months in terms of the period in which participants were signing consents. The 18 month estimate covered from initial contact with potential recruiters and participants until final data collection.
Discrepancy		Numbers recruited and recruitment period
Action rule	2	Numbers recruited taken as 61- as 61 consented and recruited to the study though 7 were excluded later

		as did not meet the inclusion criteria.

Dolphin study 1

Target sample size	60	Original sample size 60 as per NIHR report and CI
UK recruitment	62	61 as per NIHR data and 62 as per CI
Target recruitment period (months)	24	27 months as per original opening and closing dates in NIHR report and 24 months as per CI
Actual recruitment period (months)	33	33 months
Recruitment success (P)	S	Recruited to 100% target
Recruitment success (S)	U	Recruited to 100% target in a period exceeding 10% of the planned recruitment period
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	Y	both
Extension granted	Y	Recruitment into the Study was intended to run for 2 years from 2009 but was slow to start. The first recruit did not enter until April 2010 and by the end of the year only 15 recruits had joined. An extension to recruitment was sought from and approved by the University's R&D Dept. in 2011 and additional funds were agreed by both the Study's Charitable Sponsors.
Discrepancy		Target recruitment period
Action rule	1	

Dolphin study 2

Target sample size	60	Original sample size 60 as per NIHR report and CI
UK recruitment	40	40 as per NIHR data and CI
Target recruitment period (months)	24	38 months as per original opening and closing dates in NIHR report and 24 months as per CI
Actual recruitment period (months)	50	50 months
Recruitment success (P)	U	Did not recruit to 100% target
Recruitment success (S)	U	Did not recruit to 100% target
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	Y	both
Extension granted	Y	
Notes (CI questionnaire)		Recruitment into this cohort of the study proved problematic from the outset. It was primarily dependent on the referral of potential recruits by Community Paediatric Consultants who had agreed to act as Study Collaborators. Some proved better than others and remembering the study and mentioning it to families attending their clinics. Additionally, it is also suspected that eventual success in recruiting into the Dolphin I cohort had the effect of reducing the potential recruits into this cohort.
Discrepancy		Target recruitment period
Action rule	1	

Evaluation of Telephone Administered CBT for Young People with OCD

Target sample size	72	Original sample size 80 as per NIHR report and not mentioned in CI response

UK recruitment	72	72 as per NIHR data and CI
Target recruitment period (months)	24	27 months as per original opening and closing dates in NIHR report and 24 months as per CI
Actual recruitment period (months)	38	38 months
Recruitment success (P)	S	
Recruitment success (S)	U	Did not recruit to 100% target
Target revised	Y	we had fewer dropouts than anticipated, so we were able to reduce the recruitment target because that allowed for drop outs within each condition
Recruitment discontinued earlier than planned	N	
Extension requested	Y	both
Extension granted	Y	extension was requested because of the slower than expected rate of recruitment
Discrepancy		Target sample size and target recruitment period
Action		Revised target of 72 accepted as target sample size as this was a result of a reduced dropout rate.

i- BASIS

Target sample size	50	Original sample size 50 as per NIHR report and CI
UK recruitment	54	52 as per NIHR data and 54 as per CI
Target recruitment period (months)	10	17 months as per original opening and closing dates in NIHR report and 10 months as per CI
Actual recruitment period (months)	21	21 months
Recruitment success (P)	S	
Recruitment success (S)	U	
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	Y	no cost extension
Extension granted	Y	Slow initial recruitment, interference from the Olympics
Discrepancy		Numbers recruited and target recruitment period
Action rule	1	

IMPACT

Target sample size	540	Original sample size 540 as per NIHR report
UK recruitment	472	472 as per NIHR data
Target recruitment period (months)	19	19 months as per original opening and closing dates in NIHR report
Actual recruitment period (months)	31	31 months
Recruitment success (P)	U	
Recruitment success (S)	U	
Target revised		Information not available
Recruitment discontinued earlier than planned		Information not available
Extension requested		Information not available
Notes		CI has not responded to the questionnaire

Intervention for Parents with Young Asthmatic Children

Target sample size	180	Original sample size 180 as per NIHR report
UK recruitment	136	136 as per NIHR data
Target recruitment period (months)	24	24 months as per original opening and closing dates in NIHR report
Actual recruitment period (months)	23	23 months
Recruitment success (P)	U	
Recruitment success (S)	U	
Target revised		Information not available
Recruitment discontinued earlier than planned		Information not available
Extension requested		Information not available
Notes		CI has not responded to the questionnaire

Kneeblock Study

Target sample size	110	Original sample size 100 as per NIHR report and 110 as per CI
UK recruitment	40	1 as per NIHR data and 40 as per CI
Target recruitment period (months)	24	70 months as per original opening and closing dates in NIHR report and 24 months as per CI
Actual recruitment period (months)	17	17 months
Recruitment success (P)	U	
Recruitment success (S)	U	
Target revised	N	
Recruitment discontinued earlier than planned	Y	Because of lack of recruitment
Extension requested	N	
Discrepancy		Target sample size and recruitment period, numbers recruited
Action rule	1	

LEAP study

Target sample size	640	Original sample size 640 as per NIHR report and 480 as per CI
UK recruitment	640	111 as per NIHR data and 640 as per CI
Target recruitment period (months)	30	23 months as per original opening and closing dates in NIHR report, 24 months for target of 480 and 30 months for revised target of 640
Actual recruitment period (months)	30	30 months
Recruitment success (P)	S	
Recruitment success (S)	S	
Target revised	Y	Initial powering of study was potentially compromised by high number of patients screened with pre-existing peanut allergy
Recruitment discontinued earlier than planned	N	
Extension requested	Y	No cost extension
Extension granted	Y	Time extension only, to complete final study visits
Notes (Information from study team)		The originally approved LEAP Study protocol (September 2006) had a target sample size of 480. This was revised in 2008 and increased to 640. The target sample was amended accordingly in the NIHR database. We proceeded to recruit 640 participants

		into the LEAP Study, with recruitment coming to an end in May 2009. Unfortunately we were only able to enter the last 111 of these 640 participants into the UKCRN/NIHR database, due to technical limitations of the online accrual system introduced at the time.
Discrepancy		Target sample size and recruitment period
Action rule	2	

NIRS

Target sample size	30	Original sample size 30 as per NIHR report and checked with NIHR data manager, 32 as per CI
UK recruitment	12	16 as per NIHR data, 12 running total in NIHR spreadsheet, 7 as per CI
Target recruitment period (months)	12	23 months as per original opening and closing dates in NIHR report and 12 months as per CI
Actual recruitment period (months)	30	30 months
Recruitment success (P)	U	Did not recruit to 100% target
Recruitment success (S)	U	Did not recruit to 100% target
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	N	
Notes (CI questionnaire)		a) Recruitment proved very difficult. b) The equipment used for respiratory measurements had unforeseen technical issues
Discrepancy		Target sample size and recruitment period, numbers recruited
Action rule	1	

Nitric Oxide levels

Target sample size	150	Original sample size 150 as per NIHR report and CI
UK recruitment	90	96 as per NIHR data and 90 as per CI
Target recruitment period (months)	12	25 months as per original opening and closing dates in NIHR report and 12 months as per CI
Actual recruitment period (months)	23	23 months
Recruitment success (P)	U	
Recruitment success (S)	U	
Target revised	Y	'Recruitment was challenging. Alpha level was revised from 2.5 to 5% reducing the required number to 90'
Recruitment discontinued earlier than planned	N	
Extension	N	
Discrepancy		Target recruitment period and numbers recruited
Action rule	2	

Optigrow Infant feeding study

Target sample size	500	Original sample size 500 as per NIHR report and 90 as per CI, 500 as checked with NIHR data manager
UK recruitment	647	633 as per NIHR data and 647 as per CI
Target recruitment period	24	32 months as per original opening and closing dates

(months)		in NIHR report and 24 months as per CI
Actual recruitment period (months)	31	31 months
Recruitment success (P)	S	recruited to 100% target
Recruitment success (S)	S	
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	Y	No cost extension
Extension granted	Y	In order to continue to follow-up children
Discrepancy		Target sample size and recruitment period, numbers recruited
Notes (Information from CI)		The numbers recruited were 647 which is higher than target but since this is a long term study, permission was obtained to continue recruiting to ensure adequate numbers at FU many years down the line
Action rule	1,2	

PACT

Target sample size	144	Original sample size 144 as per NIHR report and 147 as per CI
UK recruitment	152	163 as per NIHR data and 152 as per CI
Target recruitment period (months)	19	15 months as per original opening and closing dates in NIHR report and 24 months as per CI
Actual recruitment period (months)	19	months
Recruitment success (P)	S	recruited to 100% target
Recruitment success (S)	S	recruited to 100% target
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	Y	no cost extension for 6 months due to recruitment rate
Extension granted	Y	
Discrepancy		Target sample size and recruitment period, numbers recruited
Notes (Information from CI)		144 target, 152 recruited in 19 months, target recruitment period 19 months
Action rule	2	

Pilot RCT comparing Surgery to Observation for Intermittent Exotropia

Target sample size	144	Original sample size 240 as per NIHR report and 144 as per CI
UK recruitment	49	49 as per NIHR data and CI
Target recruitment period (months)	6	3 months as per original opening and closing dates in NIHR report and 6 months as per CI
Actual recruitment period (months)	8	8 months
Recruitment success (P)	U	
Recruitment success (S)	U	
Target revised	N	Did not recruit to 100% target but did not close earlier than planned
Recruitment discontinued earlier than planned	N	

Extension requested	Y	No cost extension for 3 months due to poor recruitment
Extension granted	Y	
Discrepancy		Target sample size and recruitment period, numbers recruited
Action rule	1	

Preventing asthma exacerbations by avoiding mite allergen

Target sample size	284	Original sample size 450 as per NIHR report and 284 as per CI
UK recruitment	284	434 as per NIHR data and 284 as per CI
Target recruitment period (months)	18	18 months as per original opening and closing dates in NIHR report and 12-18 months as per CI
Actual recruitment period (months)	16	16 months
Recruitment success (P)	S	
Recruitment success (S)	S	
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension	N	
Notes (Information from CI)		Target sample size 284 (450 consented to be able to randomise 284) and 284 randomised. The NIHR

STATbiTR

Target sample size	30	Original sample size 36 as per NIHR report and 30 as per CI
UK recruitment	35	38 as per NIHR data and 35 as per CI
Target recruitment period (months)	24	24 months as per original opening and closing dates in NIHR report and CI has not reported
Actual recruitment period (months)	17	17 months
Recruitment success (P)	S	
Recruitment success (S)	S	
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension	N	
Notes		Questionnaire completed by Research assisstant involved at the end of the study. CI on long term sick leave
Discrepancy		Target sample size and numbers recruited
Action rule	1	

Study of Tolerance to Oral Peanut

Target sample size	104	Original sample size 104 as per NIHR report and CI
UK recruitment	104	104 as per NIHR data and CI
Target recruitment period (months)	12	48 months as per original opening and closing dates in NIHR report and 12 months as per CI
Actual recruitment period	35	35 months

(months)		
Recruitment success (P)	S	
Recruitment success (S)	U	
Target revised	N	
Recruitment discontinued earlier than planned	N	
Extension requested	Y	no cost extension
Extension granted	Y	Limited capacity to undertake research procedures on research ward
Discrepancy		Target recruitment period
Action	1	

Telephone consultations for children with inflammatory bowel disease

Target sample size	92	Original sample size 92 as per NIHR report
UK recruitment	86	86 as per NIHR data
Target recruitment period (months)	37	37 months as per original opening and closing dates in NIHR report and CI has not reported
Actual recruitment period (months)	12	12 months
Recruitment success (P)	U	
Recruitment success (S)	U	
Target revised		Information not available
Recruitment discontinued earlier than planned		Information not available
Extension		Information not available
Notes		CI has not responded to questionnaire.

Use of sensory blankets for children with autistic spectrum disorder

Target sample size	70	Original sample size 100 as per NIHR report and CI, planned sample size 70
UK recruitment	85	72 as per NIHR data and 85 as per CI
Target recruitment period (months)	18	18 months as per original opening and closing dates in NIHR report and CI
Actual recruitment period (months)	10	10 months
Recruitment success (P)	S	
Recruitment success (S)	S	
Target revised	Y	One revision was made as dropout rate was less than anticipated
Recruitment discontinued earlier than planned	N	
Extension requested	N	
Notes		Recruitment started later than anticipated, but all ran within the timeframe of the trial.
Discrepancy		Target sample size and numbers recruited
Action	1	Revised target accepted as revised due to a reduced dropout rate

Appendix 9: Covering letter for questionnaire sent to Chief Investigators (Chapter 3)

We are conducting a study to investigate what factors affect recruitment to clinical trials with children. This study is part of the work of the MRC North West Hub for Trials Methodology Research and is being undertaken by our clinical PhD student, Geetinder Kaur. We are conducting a review of recruitment to paediatric trials on the NIHR portfolio and would like to ask you for a small amount of information about the trial which you have led.

All information provided will be strictly confidential. Please note that while we need to know the trial details for data management purposes, no individual or trial will be identified in any publication.

The questionnaire is short and will only take about 10 minutes to complete via the following link http://edu.surveygizmo.com/s3/1263672/NIHR-portfolio-review-questionnaire. Please answer all questions and submit the questionnaire by 15th June 2013.

Please feel free to contact us, by e-mail to gkaur@liv.ac.uk, if you experience any technical difficulties or have any queries about completing the questionnaire.

Many Thanks

Kind Regard

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Liverpool L69 3GS

Appendix 10: Questionnaire sent to Chief Investigators in NIHR portfolio review (Chapter 3)

1) Name of the trial*

_____

2) Please enter your name and role in the trial*

_____

3) What was the design of the trial?
( ) Parallel
( ) Factorial
( ) Crossover
( ) Other

Please specify_____

4) Was the trial
( ) individually randomised
( ) cluster randomised
( ) other

5) Please specify_____

---

6) What was the clinical setting for recruitment?
Please hold 'ctrl' key for Windows and 'cmd' key for Mac, when clicking on options to select multiple options
( ) Outpatient clinic
( ) Paediatric Ward
( ) Children's Accident & Emergency
( ) Accident & Emergency Department
( ) Paediatric Intensive Care Unit
( ) Neonatal Intensive Care Unit
( ) Postnatal Ward
( ) General practice
( ) Community clinic
( ) School
( ) Other

Other (please specify)_____

7) Was blinding implemented?
( ) Yes
( ) No

Who was blinded?
[ ] Patients
[ ] Health care providers
[ ] Data collectors
[ ] Outcome adjudicators
[ ] Data analysts
[ ] Other

Please specify_____

8) Was the primary outcome measure available from routinely collected data such as patient notes or electronic records?
( ) Yes
( ) No

What was the method of data collection for primary outcome variable?

---

9) What was the total number of participants recruited to the trial?
_____

10) What was the sample size in original approved protocol?
_____

11) Was this revised during the course of the trial?
( ) Yes
( ) No

Please give details, including the number of revisions, final recruitment target and the reasons for revision.
_____

12) What was the planned duration for recruitment in the original approved protocol?
_____

13) Was trial recruitment discontinued earlier than planned?
( ) Yes
( ) No

Please give reasons_____

14) Was a trial extension requested?
( ) Yes
( ) No

Was the request for a
( ) cost extension (extension of trial grant)
( ) no cost extension (time only extension)
( ) Both

Was the extension granted?
( ) Yes
( ) No

Please give details including reasons for requesting a trial extension?
_____

Additional comments, if any

---

15) Based on trial protocol, did the participant or parent/carer have to undergo any of the following as a part of the trial, which was outside of routine clinical practice?
Please hold the 'ctrl' key for Windows and 'cmd' key for Mac, when clicking on options to select multiple options.
( ) Additional painful/invasive procedure for trial that would not happen otherwise

( ) Extra blood tests i.e. additional venepuncture event that would otherwise not be necessary
( ) Extra blood taken with routine bloods
( ) Any other extra tests/procedure
( ) Additional hospital/clinic visit for protocol defined follow up
( ) Additional/prolonged clinic visits
( ) Extended hospital stay
( ) Extra travel cost
( ) Extra travel distance/ time
( ) Extra days off work for family/young adult
( ) Extra days off school
( ) Change in lifestyle of child/young adult/family
( ) Extra paperwork for child/young adult/family e.g. questionnaires, treatment diaries etc.
( ) Other
( ) None

Please give relevant details_____

---

16) Did the trial have Clinical Trials Unit (CTU) support?
( ) Yes
( ) No

Name of the CTU
_____

Is the CTU UKCRC registered?
( ) Yes
( ) No

What was the nature and degree of support provided by the CTU?
Please hold the 'ctrl' key for Windows and 'cmd' key for Mac, when clicking on options to select multiple options.
( ) Advice on trial design
( ) Costing of the trial and planning of staffing required to develop and manage the trial
( ) Communication with the Clinical Research Networks regarding feasibility and levels of interest
( ) Management of the trial
( ) Liaising with potential centres, identifying and initiating participating centres, and maintaining good communication with each centre
( ) Recruiting clinical sites in order to identify and recruit eligible trial patients and allocating a trial entry number and treatment to trial patients
( ) Data management
( ) Trial monitoring
( ) Conducting interim and final analyses
( ) Other

Please specify_____

17) Did the trial have a trial coordinator/manager?
( ) Yes
( ) No

Was the trial coordinator/manager
( ) Employed within the CTU
( ) Research fellow
( ) Chief Investigator
( ) Other

Please give relevant details_____

Was the trial coordinator
( ) Full time equivalent throughout the trial
( ) Less than full time
( ) Other

What % of full time equivalent?
_____

Please give details

---

18) Was a pilot study or feasibility assessment conducted prior to starting the trial?
( ) Yes
( ) No
( ) Not applicable as the trial itself is a pilot/feasibility study

What was the nature of the study?
( ) Pilot study
( ) Feasibility assessment

Please describe the 'design, aims and methods' of the pilot study
_____

Please describe the 'design, aims and methods' of the feasibility assessment
_____

19) Did it lead to any change in the recruitment target or recruitment strategy?
( ) Yes
( ) No

Please specify_____

Thank You!
Many thanks for providing this information. Your response is very important to us.

Appendix 11: Recruitment information from various sources for International studies in NIHR portfolio review (Chapter 3)

SR	Study	Global sample size		Enrolment (Clinical Trials.gov)	Sample size (CI)	Recruitment (CI)	Study start date (ClinicalTrials.gov)	Primary completion date (final data collection date for POM) (ClinicalTrials.gov)
		UKCRN portfolio	NIHR study report					
1	Can we Reduce the Number of Vaccine Injections for Children?	498	498	Estimated enrolment 498	384	509 (confirmed with study team)	Jan 2010	June 2013 Recruitment stopped 280113
2	CASG 112	106	106	109	104	109	June 2008	Dec 2011
3	MCRN 000	54	54	79		Not responded	Sept 2006	Nov 2008
4	MCRN 003	300	300	306	306	306	June 2007	Sept 2008
5	MCRN 011	108	108	112	5	5	May 2008	Sep 2009
6	MCRN 014	184	184	192	80	1	April 2007	May 2010
7	MCRN 017	120	120	139	120	137	July 2008	Nov 2009
8	MCRN 018	266	266	207		Not responded	Dec 2008	March 2011
9	MCRN 020	720	720	719	70	0	July 2008	Aug 2012
10	MCRN 023	1885	1800	1467	1885	1800	Aug 2008	July 2010
11	MCRN 024	333	333	336	336	336	Oct 2008	April 2011
12	MCRN026	100	100	101	100	101	March 2009	Aug 2012
13	MCRN 042	252	252	304		Not responded	Dec 2007	Aug 2012
14	MCRN 049	185	185	188		Not responded	Nov 2009	Jan 2013
15	MCRN 052	1550	1550	1579	1550	1582	March 2009	May 2011
16	MCRN 057	620	620	1000 e	620	812	Jan 2010	Sep 2015 Recruitment stopped Oct 2010
17	MCRN067	214	214	177	5	4	July 2009	Sep 2011

18	MCRN 071	900	900	1382	Not responded		Nov 2009	April 2011
19	MCRN 076	32	32	31	1	1	Aug 2009	July 2010
20	MCRN 084	60	60	52 (Target 30 in CTR)	30	52	Aug 2009	Nov 2010
21	MCRN 105	180	180	228	6	10	July 2010	March 2013
22	MCRN 112	510	510	528	510	528	May 2010	June 2013, Recruitment stopped 22 March 2013
23	MCRN 119	16	16	16	12	14	Nov 2009	Oct 2012
24	MCRN 128	90	90	90	Not responded			
25	MCRN 129	210	210	215	3	3	Apr 2011	March 2013
26	MCRN 142	150	150	110	3	3	May 2010	Jan 2013
27	MCRN 144	8200	8200	12000	Not responded		Oct 2011	Jan 2015
28	MCRN 153	346	346	350	6	4	Jan 2012	July 2013
29	MCRN 171	75	75	92	75	75	March 2012	Jan 2014 Recruitment stopped Jan 2013
30	NCRN 308	300	300	307	Not responded		Sep 2011	March 2013
31	PENTA 18	160	160	173	160	173	Aug 2010	July 2012

Appendix 12: Study details of identified MCRN studies in NIHR portfolio review (Chapter 3)

SR. No.	Portfolio Study ID	Study Acronym / Short Title	Study Title	Active Status	Randomisation ?	Actual Opening Date	Actual Closure Date
1	**2312**	ADEPT	Abnormal Doppler Enteral Prescription Trial	Closed - follow-up complete	Randomised	01/04/2006	31/05/2009
2	**3217**	Amitriptyline in EB Pain	Double blind, placebo controlled crossover study of the efficacy and side effects of low dose amitriptyline treatment for chronic pain, disordered sleep and reduced mobility in children with Epidermolysis Bullosa	Closed - follow-up complete	Randomised	26/09/2006	12/02/2010
3	**12221**	An alternative booster vaccine against meningitis and ear infections	A phase III randomised, open label clinical trial evaluating the immunogenicity of a 10-valent pneumococcal conjugate vaccine booster compared to the standard 13-valent pneumococcal conjugate vaccine booster given at 12 months of age to healthy children who have received the 13-valent pneumococcal conjugate vaccine at 2 and 4 months of age.	Closed - in follow-up	Randomised	05/04/2012	07/09/2012
4	**7544**	BEEP	Feasibility Study of Barrier Enhancement for Eczema Prevention	Closed - in follow-up	Randomised	22/03/2010	31/01/2011
5	**2231**	BOOST II UK	Which oxygen saturation level should we use for very premature infants? A randomised controlled trial	Closed - in follow-up	Randomised	29/09/2007	24/12/2010
6	**11354**	Bronchiolitis of Infancy Discharge Study (BIDS).	Bronchiolitis of Infancy Discharge Study (BIDS).	Closed - in follow-up	Randomised	03/10/2011	31/03/2013
7	**8976**	Can we Reduce the Number of Vaccine	An open label randomised controlled study to evaluate the induction of immune memory	Closed - in follow-up	Randomised	13/07/2010	29/07/2011

		Injections for Children?	following infant vaccination with a glyco-conjugate Neisseria meningitidis serogroup C vaccine and to assess the immune response to the concurrent infant routine immunisations administered in consistent versus alternating limbs.				
8	**4506**	CASCADE	Maximising engagement, motivation and long term change in a Structured Intensive Education Programme in Diabetes for children, young people and their families: Child and Adolescent Structured Competencies Approach to Diabetes Education	Closed - follow-up complete	Randomised	01/02/2009	18/09/2010
9	**5799**	CASG112	A Phase III, Randomized, placebo-controlled, blinded investigation of six weeks vs. six months of oral valganciclovir therapy in infants with symptomatic congenital cytomegalovirus infection (CASG 112)	Closed - in follow-up	Randomised	04/04/2011	16/06/2011
10	**7976**	CATCH	A randomised controlled trial comparing the effectiveness of heparin bonded or antibiotic impregnated central venous catheters with standard conetral venous catheters for the prevention of hospital acquired blood stream infection in children	Closed - in follow-up	Randomised	25/11/2010	30/11/2012
11	**9601**	CCRN 415 (Haemophilia A)	A-LONG: An Open-label, Multicenter Evaluation of the Safety, Pharmacokinetics, and Efficacy of Recombinant Factor VIII Fc Fusion (rFVIIIFc) in the Prevention and Treatment of Bleeding in Previously Treated Subjects With Severe Haemophilia A	Closed - in follow-up	Randomised	10/10/2011	09/12/2011
12	**10035**	CCRN 470 (Haemophilia)	A multi-centre, single-blind trial evaluating the safety and efficacy, including pharmacokinetics, of NNC-0156-0000-0009	Closed - in follow-up	Randomised	26/04/2011	20/02/2012

			when used for treatment and prophylaxis of bleeding episodes in patients with haemophilia B				
13	**10451**	CCRN 515 (Acute pain)	A randomised, double blind, multi-centre, placebo controlled study to evaluate the efficacy and safety of methoxyflurane (PenthroxT) for the treatment of acute pain in patients presenting to an Emergency Department with minor trauma	Closed - in follow-up	Randomised	14/07/2011	03/08/2012
14	**3218**	CHIP Trial	Control of Hyperglycaemia in Paediatric Intensive Care: The CHIP Trial	Closed - in follow-up	Randomised	07/04/2008	31/08/2011
15	**11447**	Closing the loop in adolescents during non-compliance behaviours	An open-label, single-centre, randomised, 2-period cross-over study to assess the efficacy and safety of 24-hour closed-loop glucose control in comparison with conventional subcutaneous insulin pump treatment simulating noncompliant behaviours in adolescents with type 1 diabetes	Closed - in follow-up	Randomised	01/12/2011	30/04/2012
16	**9111**	Cognative GA Study - TIVA versus volatile anaesthesia in children: cognitive effects	Randomised clinical trial of the effects of total intravenous anaesthesia (TIVA:propofol) versus volatile anaesthesia (sevoflurane:nitrous oxide) on children's post-operative cognition, behaviour and physical morbidity.	Closed - follow-up complete	Randomised	01/02/2007	31/05/2010
17	**9530**	CRITIC-1	Circadian Rhythm in Tobramycin Elimination in Cystic Fibrosis CRITIC-1	Closed - follow-up complete	Randomised	10/05/2011	08/01/2013
18	**4171**	DECIDE	Delivering Early Care in Diabetes Evaluation: An RCT to assess hospital versus home management at diagnosis in childhood diabetes	Closed - in follow-up	Randomised	09/07/2008	31/10/2011
19	**3837**	DEPICTED	Development and Evaluation of a Psychosocial Intervention for Children and Teenagers Experiencing Diabetes	Closed - in follow-up	Randomised	14/01/2008	30/11/2008

20	**3777**	DRN067 (FACTS)	A randomised controlled trial to examine whether enhanced family commmunication improves glycaemic control in adolescents with type 1 diabetes	Closed - follow-up complete	Randomised	24/10/2007	14/10/2009
21	**5015**	DRN191 KICk-OFF	A multi-centre, randomised controlled trial comparing intensive structured education with standard education in 11-16 year olds on intensive insulin therapy	Closed - in follow-up	Randomised	04/02/2009	23/06/2010
22	**6060**	DRN229 (MCRN028)	A Phase III, 3-Arm, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study, to Investigate the Impact of Diamyd® on the Progression of Diabetes in Patients Newly Diagnosed with Type 1 Diabetes Mellitus.	Closed - follow-up complete	Randomised	29/11/2008	30/04/2009
23	**7390**	DRN359	DRN 359- A 16-week, randomised, controlled, open label, multicentre, multinational, three-arm, parallel, treat-to target trial comparing efficacy and safety of three different dosing regimens of either SIBA or insulin glargine (Lantus®) administered as once daily basal-bolus insulin all in combination with standard pre-meal bolus insulin in subjects with type 1 diabetes mellitus currently well controlled on basal bolus insulin regimens	Closed - follow-up complete	Randomised	03/03/2010	26/05/2010
24	**6092**	EPIC Project	Evidence into practice: evaluating a child-centred intervention for diabetes medicine management.	Closed - in follow-up	Randomised	16/02/2010	11/08/2011
25	**2311**	EVERT	Cryotherapy versus salicylic acid for the treatment of verrucae: A randomised controlled trial	Closed - follow-up complete	Randomised	08/11/2006	08/01/2010
26	**3221**	GAP Study	A randomised controlled trial of garlic as a quorum sensing inhibitor in patients with cystic fibrosis and chronic Pseudomonas	Closed - follow-up complete	Randomised	24/04/2007	25/09/2007

			aeruginosa				
27	**6635**	GAS	A multi-site RCT comparing regional and general anaesthesia for effects on neurodevelopmental outcome and apnoea in infants	Closed - in follow-up	Randomised	01/10/2009	31/01/2013
28	**6377**	Glutamine in CF	Glutamine supplementation for cystic fibrosis: a parallel group randomized controlled trial	Closed - follow-up complete	Randomised	01/04/2009	31/03/2011
29	**7464**	H1N1	Open Label Randomized Parallel-Group Multi-Centre Study to Evaluate the Safety, Tolerability and Immunogenicity of Baxter H1N1 vaccine and GlaxoSmithKline H1N1 vaccine in children 6 months to 12 years of age.	Closed - follow-up complete	Randomised	24/09/2009	31/10/2009
30	**7552**	I2S2	A randomised control trial of iodine supplementation in preterm infants.	Closed - in follow-up	Randomised	10/03/2010	31/12/2012
31	**8814**	INDIGO - Pump versus MDI insulin and hypoglycaemia in children.	"INDIGO - ""Tight glycaemic control"" and the risk of hypoglycaemia: Is this different between multiple injections versus insulin pump therapy? A UK multi-centre, open randomised control trial."	Closed - follow-up complete	Randomised	01/04/2008	04/11/2010
32	**7553**	KONCERT (PENTA18)	A study of the pharmacokinetics, safety and efficacy of twice-daily versus once-daily lopinavir/ritonavir tablets dosed by weight as part of combination antiretroviral therapy in HIV-1 infected children.	Closed - in follow-up	Randomised	07/08/2010	24/08/2012
33	**2276**	MAGNETIC	MAGnesium NEbuliser Trial In Children - A randomised controlled trial of nebulised magnesium in acute severe asthma in children	Closed - follow-up complete	Randomised	04/12/2008	21/03/2011
34	**9932**	MAMA	Measures to address maternal anxiety	Closed - in follow-up	Randomised	01/03/2011	19/12/2012
35	**3774**	MASCOT	Management of Asthma in School Age	Closed - in	Randomised	01/01/2009	30/06/2010

			Children on Therapy	follow-up			
36	**2736**	MCRN000 (MEE103219)	A Randomized, Double-Blind, Parallel Group Clinical Trial to Assess Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Intravenous Mepolizumab (SB240563)(0.55mg/kg, 2.5mg/kg or 10mg/kg) in Pediatric Subjects With Eosinophilic Esophagitis, Aged 2 to 17 Years (Study MEE103219)	Closed - follow-up complete	Randomised	01/09/2006	07/03/2008
37	**2525**	MCRN001 (DPM-CF-301)	Long Term Administration Of Inhaled Dry Powder Mannitol In Cystic Fibrosis - A Safety And Efficacy Study	Closed - follow-up complete	Randomised	01/07/2007	15/08/2008
38	**3297**	MCRN002 (6096A1-007)	A Phase 3, Randomized, Active-Controlled, Double-Blind Trial Evaluating The Safety, Tolerability, And Immunogenicity Of A 13-Valent Pneumococcal Conjugate Vaccine In Healthy Infants Given With Routine Pediatric Vaccinations In The United Kingdom	Closed - follow-up complete	Randomised	01/10/2006	12/06/2007
39	**3826**	MCRN003 (MK0954-326)	A Randomized, Double-Blind, Parallel, Placebo- Or Amlodipine-Controlled Study Of The Effects Of Losartan On Proteinuria In Pediatric Patients With Or Without Hypertension	Closed - follow-up complete	Randomised	31/10/2007	28/05/2008
40	**4108**	MCRN008 (A6281287)	A Two-Year Multi-Centre, Randomized Two Arm Study Of Genotropin Treatment In Very Young Children Born Small For Gestational Age: Early Growth And Neurodevelopment (EGN)	Closed - follow-up complete	Randomised	19/08/2008	08/02/2010
41	**4497**	MCRN011 (WA18221)	A 12-week randomized, double blind, placebo-controlled, parallel group, 2-arm study to evaluate the efficacy and safety of tocilizumab in patients with active systemic	Closed - follow-up complete	Randomised	16/10/2008	02/06/2009

			juvenile idiopathic arthritis (sJIA); with a 92-week single arm open-label extension to examine the long term use of tocilizumab				
42	**4614**	MCRN012 (PTC124-GD-007-DMD)	A Phase 2b Efficacy and Safety Study of PTC124 in Subjects with Nonsense-Mutation-Mediated Duchenne and Becker Muscular Dystrophy	Closed - follow-up complete	Randomised	28/07/2008	05/01/2009
43	**4615**	MCRN014 (M06-806)	A Multi-center, Double-blind Study to Evaluate the Safety, efficacy and Pharmacokinetics of the Human Anti-TNF Monoclonal Antibody Adalimumab in Paediatric Subjects with Moderate to Severe Crohn's Disease.	Closed - follow-up complete	Randomised	24/10/2008	24/04/2009
44	**5641**	MCRN016 (205.339)	A randomized, double-blind, placebo-controlled parallel group study to investigate the safety and efficacy of two doses of tiotropium bromide (2.5 µg and 5 µg) administered once daily via the Respimat® device for 12 weeks in patients with cystic fibrosis	Closed - follow-up complete	Randomised	10/10/2008	15/12/2009
45	**5716**	MCRN017 (A6111137)	A Phase 3 Prospective, Randomized, Double-Masked, 12-Week, Parallel Group Study Evaluating The Efficacy And Safety Of Latanoprost And Timolol In Paediatric Subjects With Glaucoma	Closed - follow-up complete	Randomised	28/11/2008	16/06/2009
46	**4739**	MCRN018 (E2090-E044-312)	A double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy and safety of adjunctive zonisamide in paediatric partial onset seizures	Closed - follow-up complete	Randomised	12/03/2009	30/09/2010
47	**5788**	MCRN020 (MI-CP178)	A Phase 1/2a, Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Study to Evaluate the Safety, Tolerability, Immunogenicity and Vaccine-like Viral Shedding of MEDI-534, a Live, Attenuated	Closed - follow-up complete	Randomised	10/07/2009	18/08/2011

			Intranasal Vaccine Against Respiratory Syncytial Virus (RSV) and Parainfluenza Virus Type 3 (PIV3), in Healthy 6 to < 24 Month-Old Children and in 2 Month Old Infants				
48	**5830**	MCRN021 (E2007-G000-305)	A double-blind, placebo-controlled, dose-escalation parallel group study to evaluate the efficacy and safety of E2007 (perampanel) given as adjunctive therapy in subjects with refractory partial seizures	Closed - follow-up complete	Randomised	17/12/2008	10/06/2010
49	**5831**	MCRN023 (V72P12)	A Phase 2b, Open Label, Randomized, Parallel-Group, Multi-Center Study to Evaluate the Safety, Tolerability and Immunogenicity of Novartis Meningococcal B Recombinant Vaccine When Administered with or without Routine Infant Vaccinations to Healthy Infants	Closed - follow-up complete	Randomised	01/08/2008	07/08/2009
50	**5858**	MCRN024 (SPD489-325)	A Phase III, Randomised, Double-Blind, Multicentre, Parallel-Group, Placebo- and Active-Controlled, Dose-Optimisation Safety and Efficacy Study of Lisdexamfetamine Dimesylate (LDX) in Children and Adolescents Aged 6-17 with Attention-Deficit/Hyperactivity Disorder (ADHD)	Closed - follow-up complete	Randomised	30/09/2008	06/01/2011
51	**5906**	MCRN026 (0954_337-01)	A Phase III, Randomized, Open-Label, Parallel-Group, Dose-Ranging Clinical Trial to Study the Safety and Efficacy of MK-0954/Losartan Potassium in Paediatric Patients with Hypertension	Closed - in follow-up	Randomised	17/07/2009	24/05/2012
52	**6308**	MCRN033 (111709)	A phase II, open-label, randomized, multicentre study to evaluate the feasibility of GSK Biologicals' DTPa-IPV/Hib-MenC-TT vaccine co-administered with PrevenarT	Closed - in follow-up	Randomised	26/06/2009	08/12/2009

			compared with PediacelT co-administered with MenjugateT and PrevenarT, when given in healthy infants as a three-dose primary vaccination course at 2, 3 and 4 months of age and to evaluate MenitorixT given to these children as a booster dose at 12 months of age.				
53	**6309**	MCRN036 (PTC124-GD-009-CF)	A Phase 3 Efficacy and Safety Study of PTC124 as an Oral Treatment for Nonsense-Mutation-Mediated Cystic Fibrosis	Closed - in follow-up	Randomised	09/02/2010	24/11/2010
54	**6692**	MCRN037 (GS-US-205-0110)	An Open-Label, Randomized, Phase 3 Trial to Evaluate the Efficacy and Safety of Aztreonam 75 mg Powder and Diluent for Nebulizer Solution (AZLI) versus Tobramycin Nebulizer Solution (TNS) in an Intermittent Aerosolized Antibiotic Regimen, in subjects with Cystic Fibrosis followed by an Open-Label, Single Arm Extension	Closed - follow-up complete	Randomised	22/08/2008	23/10/2009
55	**6310**	MCRN042 (SCO/BIA-2093-305)	Efficacy and safety of eslicarbazepine acetate (BIA 2-093) as adjunctive therapy for refractory partial seizures in children a doublie-blind, randomised, placebo-controlled, parallel-group, multicentre clinical trial	Closed - in follow-up	Randomised	02/07/2009	23/12/2011
56	**8236**	MCRN043 (TRA108062)	A three part, staggered cohort, open-label and double-blind, randomized, placebo controlled study to investigate the efficacy, safety, tolerability and pharmacokinetics of eltrombopag, a thrombopoietin receptor agonist, in previously treated paediatric patients with chronic idiopathic thrombocytopenic purpura (ITP).	Closed - in follow-up	Both	28/09/2009	21/12/2012

57	**6953**	MCRN048 (V72P12E1)	A Phase 2b, Open Label, Multi-Center, Extension Study to Evaluate the Safety, Tolerability and Immunogenicity of a Booster Dose of Novartis Meningococcal B Recombinant Vaccine Administered at 12, 18 or 24 Months of Age in Subjects Who Previously Received a Three-Dose Primary Series of the Novartis Meningococcal B Recombinant Vaccine as Infants in Study V72P12	Closed - follow-up complete	Both	13/07/2009	15/07/2010
58	**7050**	MCRN049 (WA19977A)	A multi-center international study to evaluate the efficacy and safety of tocilizumab in subjects with active polyarticular-course juvenile idiopathic arthritis; followed by an open-label extension to examine the long term use of tocilizumab.	Closed - in follow-up	Randomised	23/09/2009	31/01/2011
59	**7122**	MCRN052 (MAB-N007)	A Phase 2b/3, Multi-Center, Randomized, Double-Blind, Placebo Controlled Trial to Evaluate the Safety and Efficacy of Pagibaximab Injection in Very Low Birth Weight (VLBW) Neonates for the Prevention of Staphylococcal Sepsis	Closed - follow-up complete	Randomised	22/12/2009	30/11/2010
60	**7357**	MCRN057 (GT-21)	A Randomised,parallel-group.double - blind,placebo-controlled,multi-mational,multi-centre,Phase III trial investigating the asthma preventing effect of Grazax® compared to placebo in children with grass pollen induced rhinoconjunctivitis	Closed - in follow-up	Randomised	04/01/2010	21/06/2010
61	**7299**	MCRN059 (CRAD001M2301)	A randomised, double-blind, placebo-controlled study of RAD001 in the treatment of patients with subependymal giant cell astrocytomas (SEGA) associated with Tuberous Sclerosis Complex (TSC)	Closed - in follow-up	Randomised	06/07/2010	06/08/2010

62	**7768**	MCRN067 (CACZ885G2301)	A randomized, double-blind, placebo controlled, withdrawal study of flare prevention of canakinumab (ACZ885) in patients with Systemic Juvenile Idiopathic Arthritis (SJIA) and active systemic manifestations	Closed - follow-up complete	Randomised	05/03/2010	15/11/2010
63	**7769**	MCRN068 (CACZ885G2305)	A randomized, double-blind, placebo controlled, single-dose study to assess the initial efficacy of canakinumab (ACZ885) with respect to the adapted ACR Pediatric 30 criteria in patients with Systemic Juvenile Idiopathic Arthritis (SJIA) and active systemic manifestations	Closed - follow-up complete	Randomised	05/03/2010	15/11/2010
64	**7816**	MCRN071 (082-00)	A Worldwide, Randomised, Double Blind, Placebo-Controlled, Parallel Group Clinical Trial to Evaluate the Safety and Efficacy of Rizatriptan for the Acute Treatment of Migraine in Children and Adolescents	Closed - follow-up complete	Randomised	05/05/2010	02/02/2011
65	**7985**	MCRN076 (NN8630-1824)	A randomised, open-labelled, single dose, dose-escalation trial investigating safety, tolerability, pharmacokinetics and phamacodynamics of pegylated long-acting human growth hormone (NNC126-0083) compared to Norditropin NordiFlex in growth hormone deficient children	Closed - follow-up complete	Randomised	10/11/2009	20/06/2010
66	**8030**	MCRN077 (CT0140)	A prospective, double blind randomised controlled trial to evaluate the immunological benefits and clinical effects of an elimination diet using an amino acid formula (AAF) with added pre-probiotic blend ion infants with Cow Milk Allergy (CMA).	Closed - follow-up complete	Randomised	04/03/2011	16/05/2012
67	**8309**	MCRN084 (VX08-770-103)	A Phase 3, 2 Part, Randomized, Double-Blind, Placebo Controlled, Parallel Group	Closed - in follow-up	Both	31/03/2010	06/05/2010

			Study To Evaluate The Pharmacokinetics, Efficacy And Safety Of VX 770 In Subjects Aged 6 To 11 Years With Cystic Fibrosis And The G551D Mutation				
68	**8499**	MCRN085 (DMD114117)	A phase II, double blind, exploratory, parallel-group, placebo controlled clinical study to assess two dosing regimens of GSK2402968 for efficacy, safety, tolerability and pharmacokinetics in ambulant subjects with Duchenne muscular dystrophy.	Closed - in follow-up	Randomised	28/07/2010	30/08/2011
69	**8526**	MCRN089 (111763)	A phase III, open-label, randomised multicentre study to evaluate the immunogenicity and safety of a booster dose of GlaxoSmithKline Biologicals' dTpa-IPV vaccine (Boostrix Polio) compared with Sanofi Pasteur MSD's dTpa-IPV vaccine (Repevax), when coadministered with GSK Biologicals' MMR vaccine (Priorix) in 3 and 4-year-old healthy children.	Closed - in follow-up	Randomised	04/04/2011	29/02/2012
70	**8943**	MCRN094 (NN2211-1800)	A Randomized, Double-blind, Placebo Controlled Trial to Assess Safety/Tolerability, Pharmacokinetics & Pharmacodynamics of Liraglutide in Pediatric (10 - 17 years old) and Adult Subjects with Type 2 Diabetes	Closed - follow-up complete	Randomised	09/02/2011	30/08/2011
71	**9017**	MCRN096 (205.438)	A randomised, double-blind, placebo-controlled parallel-group trial to confirm the effeicacy after 12 weeks and the safety of tiotropium 5 µg administered once daily via the Respimat® device in patients with cystic fibrosis	Closed - in follow-up	Randomised	18/01/2011	01/06/2011
72	**9460**	MCRN103 (VX10-770-106)	A Phase 2, Randomized, DoubleBlind, PlaceboControlled, Crossover Study to	Closed - in follow-up	Randomised	01/02/2011	22/08/2011

			Evaluate the Effect of VX770 on Lung Clearance Index in Subjects with Cystic Fibrosis, the G551D Mutation, and FEV1 >90% Predicted				
73	**9513**	MCRN105 (AI463-189)	A Comparative Study of the Antiviral Efficacy and Safety of Entecavir (ETV) versus Placebo in Pediatric Subjects with Chronic Hepatitis B Virus (HBV) Infection who are HBeAg-Positive	Closed - in follow-up	Randomised	09/05/2011	04/03/2013
74	**9607**	MCRN106 (MOR 004)	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multinational Clinical Study to Evaluate the Efficacy and Safety of 2.0 mg/kg/week and 2.0 mg/kg/every other week BMN 110 in Patients with Mucopolysaccharidosis IVA (Morquio A Syndrome).	Closed - in follow-up	Randomised	24/01/2011	29/02/2012
75	**10290**	MCRN112 (SPD503-315)	A phase 3 double blind placebo controlled multi centre randomised withdrawal long term maintenance of efficacy and safety study of extended release Guanfacine Hydrochloride in Children and Adolescents aged 6-17 with Attention Deficit/ Hyperactivity Disorder	Closed - in follow-up	Randomised	19/04/2011	09/07/2012
76	**9998**	MCRN119 (HGT-HIT-045)	A Phase I/II, Randomized, Safety and Ascending Dose Ranging Study of Intrathecal Idursulfase-IT Administered in Conjunction with Intravenous Elaprase? in Pediatric Patients with Hunter Syndrome and Cognitive Impairment	Closed - in follow-up	Randomised	28/02/2011	31/01/2012
77	**10291**	MCRN128 (CL2-16257-090)	Determination of the efficient and safe dose of ivabradine in paediatric patients with dilated cardiomyopathy and symptomatic chronic heart failure aged 6 months to 18 years. A placebo controlled phase II/III	Closed - in follow-up	Randomised	16/01/2012	15/02/2013

			dose-finding study with a 1 year efficacy/safety evaluation.				
78	**10292**	MCRN129 (M0001-C303)	Trial consisting of an 8-week double-blind placebo-controlled part to evaluate efficacy, safety, tolerability and pharmacokinetics of prucalopride in paediatric subjects with functional constipation, aged =6 months to <18 years, followed by a 16-week open-label comparator (PEG) controlled part, to document safety and tolerability up to 24 weeks	Closed - in follow-up	Randomised	03/08/2011	06/09/2012
79	**10616**	MCRN136 (TR02-108)	Randomised, Active-Controlled Multicenter Study to Assess the Efficacy, Safety and Tolerability of ArikaceT in Cystic Fibrosis Patients with Chronic Infection due to Pseudomonas Aeruginosa (Pa)	Closed - in follow-up	Randomised	13/03/2012	07/11/2012
80	**10907**	MCRN142 (CNTO1275PSO3006)	A Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Ustekinumab in the Treatment of Adolescent Subjects With Moderate to Severe Plaque-type Psoriasis	Closed - in follow-up	Randomised	01/12/2011	04/09/2012
81	**10909**	MCRN144 (115345)	An efficacy study of GSK Biologicals' quadrivalent influenza vaccine GSK2321138A (FLU D-QIV) when administered in children	Closed - in follow-up	Randomised	01/10/2011	30/11/2012
82	**11222**	MCRN153 (NN1250-3561)	A trial investigating efficacy and safety of insulin degludec in children and adolescents with type 1 diabetes mellitus	Closed - in follow-up	Randomised	12/03/2012	18/07/2012
83	**11587**	MCRN164 (PRI01C)	A phase III open-label randomised study, to evaluate the immunogenicity and safety of the concomitant administration of V419 (PR5I) given at 2, 3 and 4 months of age with two types of meningococcal serogroup	Closed - in follow-up	Randomised	27/02/2012	03/10/2012

			C conjugate (MCC) vaccines given at 3 and 4 months of age, followed by the administration at 12 months of age of a combined Haemophilus influenzae type b-MCC vaccine				
84	**11860**	MCRN171 (TRA115450)	A two part, double-blind, randomized, placebo-controlled and open-label study to investigate the efficacy, safety and tolerability of eltrombopag, a thrombopoietin receptor agonist, in paediatric patients with previously treated chronic immune (idiopathic) thrombocytopenic purpura (ITP)	Closed - in follow-up	Randomised	08/05/2012	03/09/2012
85	**12419**	MCRN185 (MOR-008)	A Randomized, Double-Blind, Pilot Study of the Safety and Physiological Effects of Two Doses of BMN 110 in Patients with Mucopolysaccharidosis IVA (Morquio A Syndrome)	Closed - in follow-up	Randomised	08/06/2012	24/08/2012
86	**2258**	MENDS	The use of melatonin in children with neurodevelopmental disorders and impaired sleep: an RCT	Closed - follow-up complete	Randomised	01/11/2007	07/06/2010
87	**6739**	MIGS	Microbial invasion during parenteral nutrition in surgical infants receiving glutamine	Closed - in follow-up	Randomised	21/07/2009	29/12/2011
88	**8659**	MINT	Melatonin As A Novel Neuroprotectant In Preterm Infants-Trial Study	Closed - in follow-up	Randomised	01/11/2011	09/07/2012
89	**4509**	MYCYC	A randomised clinical trial of mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA associated vasculitis	Closed - in follow-up	Randomised	12/03/2007	03/08/2011
90	**10727**	NCRN308 - Aprepitant in paediatric CINV	A Phase III, Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial, Conducted Under In-House Blinding Conditions, to Examine the Efficacy and	Closed - in follow-up	Randomised	05/03/2012	12/02/2013

			Safety of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Pediatric Patients				
91	**2522**	NEPHROTIC SYNDROME	Long-term tapering versus standard prednisolone therapy for the treatment of the initial episode of childhood nephritic syndrome: national multicentre randomised double blind pilot study	Closed - follow-up complete	Randomised	15/08/2006	01/04/2008
92	**3776**	NEST	Neonatal ECMO Study of Temperature	Closed - in follow-up	Randomised	19/06/2006	31/03/2010
93	**2502**	P3MC	A double blind, parallel group, randomised, placebo-controlled trial of Propranolol and Pizotifen in preventing migraine in children	Closed - follow-up complete	Randomised	02/02/2010	11/02/2011
94	**2313**	POP Study	Prevention and treatment of steriod-induced osteopaenia in children and adolescents with rheumatic diseases	Closed - in follow-up	Randomised	22/08/2007	30/11/2011
95	**7857**	PREPAC	Prevent pseudomonas Aeruginosa Colonisation - PREPAC	Closed - in follow-up	Randomised	01/12/2009	14/01/2011
96	**8483**	Salford Bright Smiles Baby Study	A comparison of community based preventive services to improve child dental health	Closed - in follow-up	Randomised	01/11/2010	31/12/2011
97	**6906**	SCAMP	Standardised, Concentrated, Additional Macronutrients, Parenteral (SCAMP) nutrition in preterm infants: a phase IV randomised controlled study of macronutrient intake, growth and other aspects of neonatal care	Closed - in follow-up	Randomised	01/10/2009	07/07/2012
98	**3358**	SLEEPS	Safety profile, efficacy and equivalence in paediatric intensive care sedation	Closed - follow-up complete	Randomised	18/11/2009	30/05/2012
99	**4168**	StePS	Evaluation of Corticosteroid therapy in Childhood Sepsis - a randomised pilot study	Closed - in follow-up	Randomised	27/03/2008	31/05/2012
100	**4050**	SWET	A multi-centre randomised controlled trial of	Closed -	Randomised	01/05/2007	04/06/2009

			ion-exchange water softeners for the treatment of eczema in children	follow-up complete			
101	**4507**	TAPS	Transfusion Alternatives Preoperatively in Sickle Cell Disease	Closed - follow-up complete	Randomised	20/11/2007	17/03/2011
102	**13601**	The first BCVC nasal flu vaccine study	The effects of live attenuated trivalent intranasal influenza vaccine on the nasopharyngeal bacterial colonisation in healthy children aged 2-4 years attending day care centres. A single centre, randomised, placebo-controlled intervention study.	Closed - in follow-up	Randomised	01/10/2012	29/11/2012
103	**3838**	TIPIT	A Randomised Controlled Trial of Thyroxine in Preterm Infants Under 28 weeks Gestation	Closed - in follow-up	Randomised	29/09/2007	29/04/2009
104	**2290**	TRACS	TRAining Caregivers after Stroke: A cluster randomised controlled trial of a structured training programme for caregivers of in-patients after stroke	Closed - in follow-up	Randomised	27/02/2008	09/02/2010
105	**4417**	Treatments for Childhood Crohn's Disease	Adverse Effects of Glucocorticoid Therapy on Bone in Childhood Crohn's Disease	Closed - follow-up complete	Randomised	15/11/2007	11/03/2009
106	**10016**	TROPHOS19622	Phase II, multicenter, randomized, adaptive, double-blind,placebo controlled study to assess safety and efficacy of olesoxime (TRO19622) in 3-25 year old Spinal Muscular Atrophy (SMA) patients	Closed - in follow-up	Randomised	09/03/2011	31/08/2011
107	**8869**	Wheeze and Intermittent Treatment: WAIT	Parent-Determined Oral Montelukast Therapy for Preschool Wheeze	Closed - in follow-up	Randomised	01/10/2010	19/11/2012

Appendix 13: Study details of identified Paediatric non-medicines studies in NIHR portfolio review (Chapter 3)

SR No.	Portfolio Study ID	Study Acronym / Short Title	Study Title	Active Status	Randomisation?	Actual Opening Date	Actual Closure Date
1	**6487**	07Sg35	Fat metabolism in infants and children: effects of liver dysfunction and severe infection	Closed - follow-up complete	Randomised	01/01/2008	01/02/2009
2	**6625**	A Pilot Study to Explore the Feasibility of Computerised CBT for Children	A Pilot Study to Explore the Feasibility of Computerised Cognitive Behaviour Therapy (Think, Feel, Do) for Children with Emotional Disorders	Closed - follow-up complete	Randomised	01/02/2009	28/02/2010
3	**5759**	ADOLESCENT HAYFEVER AND QUALITY OF LIFE	Cluster randomised controlled trial of an educational intervention for healthcare professionals into the management of school-age children with hayfever	Closed - follow-up complete	Randomised	29/09/2008	30/04/2010
4	**6525**	AIRS	An open randomised study of autoinflation in school age children (4-11 years) with otitis media with effusion (OME) in primary care	Closed - in follow-up	Randomised	02/02/2010	31/01/2013
5	**5025**	Assessment of Suspected Auditory Processing Disorder	Assessment of auditory and cognitive function in children with suspected auditory processing difficulties	Closed - follow-up complete		24/04/2006	24/04/2009
6	**6030**	Atomoxetine HSEN	Open label trial of Atomoxetine for Attention Deficit Hyperactivity Disorder (ADHD) in children with special educational needs	Closed - follow-up complete	Randomised	10/09/2009	30/06/2011
7	**7861**	Baby wipes trial	Baby Skin Care Research Programme: assessor blinded randomised controlled trial comparing cleansing wipes and product with water in infants	Closed - follow-up complete	Randomised	01/10/2009	22/10/2010
8	**6818**	BEADI (qualitative)	The BEADI qualitative study of clinicians views about the barriers and facilitators to using research findings to change neonatal practice (a follow on from the BLISS cluster randomised	Closed - follow-up complete	Randomised	01/05/2008	01/10/2008

			controlled trial of the effect of active dissemination and information on standards of care of premature babies in England REC 05/Q0605/180				
9	**11874**	CHAFFINCH Trial Pilot	The Chelsea Asthma and Fresh Fruit Intake in Children - Trial Pilot phase	Closed - follow-up complete	Randomised	01/08/2012	17/12/2012
10	**10428**	CLICK-EAST: The Edinburgh Autism Social-attention Trial	CLICK-EAST: Computer Learning in Children - the Edinburgh Autism Social-attention Trial	Closed - in follow-up	Randomised	23/04/2012	01/02/2013
11	**9348**	Dolphin Study 1	Optimising nutrition to improve growth and reduce neurodisabilities in neonates at risk of neurological impairment	Closed - follow-up complete	Randomised	15/04/2010	31/12/2012
12	**6797**	Dolphin Study 2	Optimising nutrition to improve growth and reduce neurodisabilities in children with suspected or confirmed Cerebral Palsy	Closed - follow-up complete	Randomised	01/12/2008	31/12/2012
13	**5279**	DRN210	A randomised, 2 period cross over study to assess the performance of post-exercise overnight computer based glucose control based on continuous subcutaneous glucose monitoring in comparison with conventional pump therapy in children and adolescents with type 1 diabetes (T1D)	Closed - follow-up complete	Randomised	01/12/2007	30/09/2008
14	**5286**	Evaluation of Telephone Administered CBT for Young People with OCD	An evaluation of the clinical effectiveness, cost-effectiveness and acceptability of a telephone-administered cognitive-behaviour therapy (CBT) program for children and young people with obsessive-compulsive disorder (OCD)	Closed - in follow-up	Randomised	01/07/2008	30/08/2011
15	**7038**	Exercise as a Treatment for Postnatal Depression	The Effectiveness of Exercise as a Treatment for Postnatal Depression	Closed - in follow-up	Randomised	01/02/2010	01/03/2012
16	**9598**	Family centred nutrition intervention in children's centres (Version 1)	Exploratory and developmental trial of a family centred nutrition intervention delivered in Children's Centres and the home environment	Closed - in follow-up	Randomised	01/11/2010	30/11/2011
17	**7738**	Feasibility study for a Schools-based, Peer-led,	Feasibility study for a schools-based, peer-led, drugs prevention programme, based on the	Closed - follow-up complete	Randomised	01/06/2007	30/11/2008

		Drugs Prevention Programme (ASSIST Programme)	ASSIST programme				
18	**9867**	FiCTION Feasibility Study	Filling Children's Teeth: Indicated or Not?	Closed - follow-up complete	Both	21/03/2011	30/04/2011
19	**6042**	FRAMEA (Framework for the Assessment of Emotional Abuse)	Does Training in a Systematic Approach to Emotional Abuse Improve the Quality of Childrens Services	Closed - follow-up complete	Randomised	01/10/2007	29/05/2009
20	**12027**	HAPPY pilot randomised controlled trial	Evaluation of an intervention to prevent childhood obesity in a bi ethnic population: the Born in Bradford NHS programme grant	Closed - in follow-up	Randomised	26/03/2012	30/11/2012
21	**10023**	Helping our premature infants on to better motor skills (HOP-ON)	Development and evaluation of a parenting intervention to promote development in infants born very premature	Closed - in follow-up	Randomised	01/03/2011	01/04/2012
22	**11188**	Home NB-UVB for focal or early vitiligo	Pilot randomised double blind controlled trial of hand held NB-UVB phototherapy for the treatment of focal or early vitiligo at home	Closed - in follow-up	Randomised	29/02/2012	31/05/2012
23	**9666**	i-BASIS	Intervention within the British Autism Study of Infant Siblings	Closed - in follow-up	Randomised	01/04/2011	31/12/2012
24	**5863**	IMPACT	Randomised controlled trial of brief psychodynamic therapy (BPP), cogntive behaviour (CBT) and active clinical care (ACC) in adolescents with moderate to severe depression attending routine child and adolescent mental health clinics	Closed - follow-up complete	Randomised	02/07/2010	31/01/2013
25	**8624**	Intervention for Parents with Young Asthmatic Children	The effects of parenting intervention on quality of life and parental confidence in management of young asthmatic children	Closed - follow-up complete	Randomised	01/06/2010	17/04/2012
26	**4227**	Kneeblock Study	Does the use of a knee block influence hip deformity, functional ability and pain in children with bilateral cerebral palsy	Closed - in follow-up	Randomised	01/01/2007	30/05/2008
27	**9469**	Later effects of promoting catch-up growth in SGA	Long-term effects of nutritional supplementation in term, small-for-gestational-age infants on bone	Closed - follow-up complete	Randomised	01/12/2010	17/02/2012

		infants	health, body composition and cognitive outcome: 16-year follow-up of a randomised, controlled trial				
28	**5823**	LEAP Study	Induction of tolerance through early introduction of peanut in high risk children	Closed - follow-up complete	Randomised	29/11/2006	29/05/2009
29	**6643**	Leptin and growth in preterm infants	Leptin, appetite, fat deposition and growth in preterm infants from birth to adolescence	Closed - follow-up complete	Randomised	01/05/2007	30/09/2009
30	**5366**	MUMS4MUMS	Structured Telephone Peer Support for Women Experiencing Postnatal Depression. Pilot and Exploratory RCT of its Clinical and Cost Effectiveness	Closed - in follow-up	Randomised	20/03/2009	30/09/2011
31	**4395**	NECOT	NECOT (North-East Cot) trial: postnatal care and breastfeeding duration	Closed - in follow-up	Randomised	07/01/2008	30/06/2009
32	**6532**	NIRS	Which is the most effective method of providing non-invasive respiratory support (NIRS) to preterm neonates with lung disease?	Closed - follow-up complete	Randomised	01/11/2008	07/09/2011
33	**6251**	Nitric Oxide Levels	Can monitoring exhaled nitric oxide levels in outpatients improve the management of children with asthma?	Closed - follow-up complete	Randomised	10/08/2006	01/07/2008
34	**8163**	Optigrow Infant Feeding Study	The Optigrow Infant Feeding Study. Effects of Early Nutrient Intake on Growth and Body Composition - A Multicentre Randomised Controlled Trial	Closed - in follow-up	Randomised	01/03/2010	04/09/2012
35	**2165**	PACT	The Pre-School Autism Communication Trial	Closed - follow-up complete	Randomised	29/06/2006	31/01/2008
36	**6094**	PATH	Psychological Advocacy towards healing: pilot for an Individually, randomised parallel group controlled trial to determine if a psychological intervention delivered by domestic violence advocates is effective and cost - effective	Closed - follow-up complete	Randomised	15/04/2009	13/11/2009
37	**9967**	Pilot RCT comparing Surgery to Observation for Intermittent Exotropia	An External Pilot Study to Test the Feasibility of a Randomised Controlled Trial comparing Eye Muscle Surgery against Active Monitoring for	Closed - in follow-up	Randomised	01/09/2011	01/05/2012

			Childhood Intermittent Distance Exotropia [X(T)]				
38	**11078**	Preventing asthma exacerbations by avoiding mite allergen	Preventing asthma exacerbations in children by avoiding mite allergen	Closed - in follow-up	Randomised	01/11/2011	22/02/2013
39	**4754**	PROMISE	PROmoting Mental health In Schools through Education - A Single Blind Randomised Controlled Trial to Determine the Effectiveness of CBT in the Prevention of Depression in High Risk Adolescents	Closed - follow-up complete	Randomised	15/12/2008	01/01/2010
40	**5642**	Proteomic Fingerprinting for RSV	Proteomic fingerprinting for Respiratory Syncytial Virus Infection in Infants and children	Closed - follow-up complete	Randomised	01/11/2007	30/09/2009
41	**12325**	REFRESH	Reducing children's exposure to second-hand smoke in the home (REFRESH)	Closed - follow-up complete	Randomised	08/02/2010	30/04/2012
42	**5734**	Regulation of mucosal immune response to systemic MenB vaccine	A phase II open label randomised single centre study to evaluate the importance of naturally induced immune regulation on the mucosal immune response to meningococcal serogroup B outer membrane vesicle (OMV) vaccine when administered intramuscularly to adults and adolescents.	Closed - follow-up complete	Randomised	01/02/2009	14/09/2012
43	**6933**	SPARCLE2	Determinants of participation and quality of life of adolescents with cerebral palsy: A longitudinal study	Closed - follow-up complete	Randomised	01/01/2009	30/06/2010
44	**6817**	STATbiTR	Effectiveness and feasibility of intensive short-term graded exercise programmes, using either treadmill or static exercise bicycle for non-ambulant children and young people with cerebral palsy in improving functional motor ability and quality of life	Closed - follow-up complete	Randomised	01/10/2008	23/02/2010
45	**7993**	Study of Tolerance to Oral Peanut	Study of Tolerance to Oral Peanut	Closed - in follow-up	Randomised	01/09/2009	31/07/2012
46	**8133**	Telephone consultations for children with	Telephone consultation as a substitute for routine out-patient face-to-face consultation for children	Closed - in follow-up	Randomised	12/07/2010	30/06/2011

		inflammatory bowel disease	with inflammatory bowel disease: randomised controlled trial and economic evaluation				
47	**8325**	The Effects of Prenatal Vitamin D Supplementation on Child Health	Effects of prenatal vitamin D supplementation on respiratory and allergic phenotypes and bone density in the first three years of life	Closed - follow-up complete	Randomised	01/03/2010	31/03/2011
48	**3813**	The EQUIP Study	Enhancing the Quality of Information-sharing in Primary care for children with respiratory tract infections.	Closed - follow-up complete	Randomised	01/09/2006	30/04/2008
49	**10663**	The impact of providing post-abortion contraceptive support	Randomised controlled study of the impact of provision of followup contraceptive support to women who have had an abortion	Closed - in follow-up	Randomised	03/10/2011	28/02/2013
50	**7402**	Towards a better understanding of hyperglycaemia in the critically ill	Towards a better understanding of hyperglycaemia in critically ill children. A sub-study of the Control of Hyperglycaemia in Paediatric intensive care (CHiP) trial.	Closed - in follow-up	Randomised	01/06/2009	31/08/2011
51	**10077**	Trial of Advice on Starting Taste Exposure (TASTE)	The impact of parental guidance on early exposure to a variety of fruit and vegetables on infants' liking and consumption	Closed - in follow-up	Randomised	28/02/2011	31/12/2011
52	**10090**	Use of sensory blankets for children with autistic spectrum disorder	Snuggledown - The use of sensory weighted blankets in children with autistic spectrum disorders and poor sleep: A randomised crossover study	Closed - in follow-up	Randomised	07/11/2011	17/09/2012

Appendix 14: Excluded MCRN and Paediatric non-medicines studies (Chapter 3)

SR	Study ID	Title	Reason for exclusion
MCRN studies			
1	7544	BEEP	no defined recruitment target
2	4506	CASCADE	cluster randomised trial
3	9601	CCRN 415 (Haemophilia A)	mixed trial; participants adults and children
4	10035	CCRN 470 (Haemophilia)	mixed trial; age range of participants 13-70 years
5	10451	CCRN 515 (Acute pain)	mixed trial; participants 5 years and older
6	11447	Closing the loop in adolescents during non-compliance behaviours	cluster randomised trial
7	9530	CRITIC-1	mixed trial; participants 12 years and older
8	3837	DEPICTED	cluster randomised trial
9	5015	DRN191 KICk-OFF	cluster randomised trial
10	7390	DRN359	participants > 18 years
11	6092	EPIC Project	mixed methods study
12	2311	EVERT	mixed trial; participants 12 years and older
13	3221	GAP Study	mixed trial; participants 8 years and older
14	6377	Glutamine in CF	mixed trial; participants 14-45 years old
15	6635	GAS	International study, recruitment period extends beyond the cut off period for inclusion in the review
16	2525	MCRN001 (DPM-CF-301)	mixed trial; participants 6 years and older
17	4614	MCRN012 (PTC124-GD-007-DMD)	mixed trial; participants 5 yrs and older
18	5641	MCRN016 (205.339)	mixed trial; participants adults and children
19	5830	MCRN021 (E2007-G000-305)	mixed trial; participants adults and children
20	6309	MCRN036 (PTC124-GD-009-CF)	mixed trial; participants adults and children
21	6692	MCRN037 (GS-US-205-0110)	mixed trial; participants adults and children
22	6953	MCRN048 (V72P12E1)	extension study
23	7299	MCRN059 (CRAD001M2301)	mixed trial; participants all ages
24	8499	MCRN085 (DMD114117)	mixed trial; participants 5 years and older

25	8943	MCRN094 (NN2211-1800)	mixed trial; participants adults and children
26	9017	MCRN096 (205.438)	mixed trial; participants adults and children
27	9460	MCRN103 (VX10-770-106)	mixed trial; participants adults and children
28	9607	MCRN106 (MOR 004)	mixed trial; participants adults and children
29	10616	MCRN136 (TR02-108)	mixed trial; participants 6 years and older
30	12419	MCRN185 (MOR-008)	mixed trial; participants adults and children
31	9932	MAMA	participants were mothers
32	8659	MINT	cluster randomised trial
33	4509	MYCYC	mixed trial; participants adults and children
34	7857	PREPAC	cluster randomised trial
35	3358	SLEEPS	cluster randomised trial
36	4507	TAPS	mixed trial; participants 1 years and older
37	10016	TROPHOS19622	mixed trial; age range of participants 3-25 years
38	2290	TRACS	cluster randomised trial, mixed trial
39	4108	MCRN 008	International study, recruitment period extended beyond the cut off period for inclusion in the review
40	8030	MCRN077	International study; up to date information on global recruitment not available
41	7769	MCRN068	International study; terminated on advice of Data Monitoring Committee
42	6060	DRN229	International study; terminated as primary end point was not met
43	8236	MCRN043	International study; global recruitment data not available

Paediatric non-medicinal studies			
1	5759	ADOLESCENT HAYFEVER AND QUALITY OF LIFE	Cluster randomised trial
2	5025	Assessment of Suspected Auditory Processing Disorder	Observational study
3	6818	BEADI (qualitative)	Observational study
4	7038	Exercise as a Treatment for Postnatal Depression	Adult participants (>18 yrs)
5	9598	Family centred nutrition intervention in children's centres (Version 1)	parents recruited
6	7738	Feasibility study for a Schools-based, Peer-led, Drugs Prevention Programme (ASSIST Programme)	Cluster randomised trial
7	9867	FiCTION Feasibility Study	observational study
8	6042	FRAMEA (Framework for the Assessment of Emotional Abuse)	Non randomised
9	12027	HAPPY pilot randomised controlled trial	participants were antenatal women and children in the first year
10	10023	Helping our premature infants on to better motor skills (HOP-ON)	Parenting intervention with participants parents of preterm infants
11	11188	Home NB-UVB for focal or early vitiligo	Participants adults and children
12	9469	Later effects of promoting catch-up growth in SGA infants	Follow up of an RCT

13	6643	Leptin and growth in preterm infants	observational study
14	5366	MUMS4MUMS	participants women with postnatal depression
15	4395	NECOT	pregnant women recruited and randomised
16	6094	PATH	mixed trial, participants women 18-40 years
17	4754	PROMISE	cluster randomised trial
18	5642	Proteomic Fingerprinting for RSV	observational study
19	12325	REFRESH	Eligible participants were mothers who smoked and had a child < 6 years old
20	5734	Regulation of mucosal immune response to systemic MenB vaccine	participants 16-40 yrs
21	6933	SPARCLE2	observational study
22	3813	The EQUIP Study	cluster randomised trial
23	7402	Towards a better understanding of hyperglycaemia in the critically ill	observational cohort study
24	6487	07Sg35	observational study
25	8325	The Effects of Prenatal Vitamin D Supplementation on Child Health	follow up of previously conducted RCT
26	10077	Trial of Advice on Starting Taste Exposure (TASTE)	mothers recruited during pregnancy or after birth
27	10663	Impact of providing post-abortion contraceptive support	Participants are women who have had an abortion
28	5279	DRN 210	Cluster randomised trial

Appendix 15: Characteristics of studies included in the NIHR portfolio review (Chapter 3)

Study ID	Study Title	Design	Setting	Blinding	Who was blinded?	POM	Source
2312	ADEPT	Parallel	Neonatal Intensive Care Unit	No		No	Paper data collection form
3217	Amitriptyline in EB Pain	Crossover	Outpatient clinic	Yes	Patients, Health care providers, Data collectors, Outcome adjudicators	No	CRF
12221	An alternative booster vaccine against meningitis and ear infections	Parallel	Other- Healthy volunteers - via Open Exeter database	Yes	Patients, Data collectors	No	Immunogenicity analysis - non-routine blood samples
2231	BOOST II UK	Parallel	Neonatal Intensive Care Unit	Yes	Patients, Health care providers, Data collectors	No	Face-to-face developmental assessments by paediatricians and age 2 years (corrected for gestation)
11354	Bronchiolitis of Infancy Discharge Study (BIDS)	Parallel	Paediatric Ward	Yes	Patients, Health care providers, Data collectors, Outcome adjudicators	Yes	
8976	Can we Reduce the Number of Vaccine Injections for Children?	Parallel	Other- Child Health departments	No		No	immunogenicity analysis on non-routine blood samples

5799	CASG112	Parallel	Paediatric Ward	Yes	Patients, Health care providers, Data collectors, Outcome adjudicators, Data analysts	No	hearing loss
7976	CATCH	Parallel	Paediatric Intensive Care Unit	No		Yes	
3218	CHIP Trial	Parallel	Paediatric Intensive Care Units	No		Yes	
9111	Cognative GA Study - TIVA versus volatile anaesthesia in children: cognitive effects	Other-randomised trial	Outpatient clinic	Yes	Patients, Data collectors, Outcome adjudicators, Data analysts	No	Standardised cognitive assessments
4171	DECIDE	Parallel	Paediatric Ward, Children's Accident & Emergency, Accident & Emergency Department	No		No	Centrally analysed HbA1c measurement.
3777	DRN067 (FACTS)	Parallel	Outpatient clinic	No		Yes	
7464	H1N1	Parallel	Other-Healthy volunteers - child Health Departments, media, emails	No		No	immunogenicity analysis from non-routine blood sampling
7552	I2S2	Parallel	Neonatal Intensive	Yes	Patients,	No	Specific face-to-face developmental

			Care Unit		Health care providers, Data collectors		assessment at age 2 years
8814	INDIGO - Pump versus MDI insulin and hypoglycaemia in children.	Information on study characteristics not available, no response from CI					
7553	KONCERT (PENTA18)	Parallel	Outpatient clinic	No		Yes	
2276	MAGNETIC	Parallel	Children's Accident & Emergency	Yes	Patients, Health care providers, Data collectors, Outcome adjudicators, Data analysts	No	Trained clinicians/nurses recording an Asthma Severity Score
3774	MASCOT	Parallel	Outpatient clinic, Children's Accident & Emergency, General practice	Yes	Patients, Health care providers, Data collectors	Yes	
2736	MCRN000 (MEE103219)	Information on study characteristics not available, no response from CI					
3297	MCRN002 (6096A1-007)	Parallel	Other- Healthy children - child health departments	Yes	Patients, Health care providers, Data collectors, Outcome adjudicators, Data analysts	No	Immunogenicity analysis - non-routine samples collected
3826	MCRN003 (MK0954-326)	Parallel	Outpatient clinic	Yes	Patients, Health care providers, Data collectors, Outcome adjudicators, Data analysts	No	Urine PCR from central lab
4108	MCRN008 (A6281287)	Crossover	Outpatient clinic	No		Yes	
4497	MCRN011 (WA18221)	Parallel	Outpatient clinic	Yes	Patients, Health care providers, Data collectors,	No	CRFs

					Data analysts		
4615	MCRN014 (M06-806)	Parallel	Outpatient clinic	Yes	Patients, Health care providers, Data collectors, Outcome adjudicators, Data analysts	No	e portfolio
5716	MCRN017 (A6111137)	Other- Stratified by age, diagnosis, and intraocular pressure (IOP) level, subjects were randomized (1:1) to latanoprost vehicle at 8 am and latanoprost 0.005% at 8 pm or timolol 0.5% (0.25% for those aged <3 years) twice daily (8 am, 8 pm).	Outpatient clinic	Yes	Patients, Health care providers, Data collectors, Outcome adjudicators, Data analysts	No	Clinical examination. Additional data was collected for the purposes of the trial.
4739	MCRN018 (E2090-E044-312)	Information on study characteristics not available, no response from CI					
5788	MCRN020 (MI-CP178)	Parallel	Outpatient clinic, Paediatric ward	Yes	Patients, Health care providers, Data collectors	No	blood sample and eCRF
5831	MCRN023 (V72P12)	Parallel	Other- Healthy volunteers - Child Health Departments	No		No	Immunogenicity analysis - non-routine blood samples collected

5858	MCRN024 (SPD489-325)	Parallel	Outpatient clinic	Yes	Patients, Health care providers, Data collectors, Outcome adjudicators	No	Interview with parents and child
5906	MCRN026 (0954_337-01)	Parallel	Outpatient clinic,	No		Yes	
6308	MCRN033 (111709)	Parallel	Other- Healthy children - Child Health Department	No		No	Immunogenicity analysis - non routine blood samples
6310	MCRN042 (SCO/BIA-2093-305)	Crossover	Outpatient clinic, Paediatric ward	Yes	Patients, health care providers	Yes	
7050	MCRN049 (WA19977A)	Information on study characteristics not available, no response from CI					
7122	MCRN052 (MAB-N007)	Parallel	Neonatal Intensive Care Unit	Yes	Patients, Health care providers, Data collectors, Outcome adjudicators, Data analysts	Yes	
7357	MCRN057 (GT-21)	Parallel	Outpatient clinic	Yes	Patients, Health care providers, Data collectors, Outcome adjudicators	No	CRF
7768	MCRN067 (CACZ885G2301)	Parallel	Outpatient clinic	Yes	Patients	No	CRF
7816	MCRN071 (082-00)	Information on study characteristics not available, no response from CI					
7985	MCRN076 (NN8630-1824)	Other-randomised, open label, single-dose, clinical trial of drug agent		Yes	Patients, Health care providers	No	specific laboratory data (PK and PD study)

8309	MCRN084 (VX08-770-103)	Parallel	Outpatient clinic	Yes	Patients, Health care providers, Data collectors, Outcome adjudicators	No	trial visit spirometry
8526	MCRN089 (111763)	Parallel	Other- participants' homes	No		No	laboratory sample
9513	MCRN105 (AI463-189)	Parallel	Paediatric Ward	Yes	Patients	Yes	
10290	MCRN112 (SPD503-315)	Parallel	Outpatient clinic	Yes	Patients, Health care providers, Data collectors, Data analysts	No	doctor collected prospectively in research appointments
9998	MCRN119 (HGT-HIT-045)	Parallel	Other- Clinical research facillity with overnight stay ability.	No		No	Yes- ultra rare disease and exploratory endpoint.
10291	MCRN128 (CL2-16257-090)	Information on study characteristics not available, no response from CI					
10292	MCRN129 (M0001-C303)	Other- Run in period (1-2.5 weeks) Double blind placebo controlled (8weeks) Open labeeled controlled period(16weeks)	Outpatient clinic	Yes	Patients, Health care providers, Data collectors, Outcome adjudicators, Data analysts	No	electronic patient diary
10907	MCRN142 (CNTO1275PSO3006)	Crossover	Outpatient clinic	Yes	Patients, Health care providers, Data collectors	Yes	
10909	MCRN144 (115345)	Parallel	General practice, Patients homes	Yes	Patients, Health care providers,	No	complicated parental reporting and sample taking from children affected

			Clinical Research Facilities		Data collectors, Outcome adjudicators, Data analysts		by colds/URTI (ie symptoms of flu)
11222	MCRN153 (NN1250-3561)	Parallel	Outpatient clinic	No		Yes	
11587	MCRN164 (PRI01C)	Parallel	Other- Participants' homes	No		No	Laboratory samples
11860	MCRN171 (TRA115450)	Parallel	Outpatient clinic	Yes	Patients, Health care providers, Data collectors, Outcome adjudicators, Data analysts	Yes	
2258	MENDS	Parallel	Outpatient clinic, paediatric ward, community clinic	Yes	All involved in the trial (patients, parents/carers, researchers, pharmacists etc...)	No	Sleep diaries and actigraphy (designed and used specifically for the study)
6739	MIGS	Parallel	Paediatric ward, Neonatal Intensive Care Unit	Yes	Patients, Health care providers, Data collectors, Outcome adjudicators, Data analysts	No	Laboratory analysis
10727	NCRN308 - Aprepitant in paediatric CINV	Parallel	Outpatient clinic, Paediatric ward	Yes	Patients, Health care providers, Data collectors	Yes	
2522	NEPHROTIC SYNDROME	Parallel	Outpatient clinic, Paediatric ward	Yes	Patients, Health care providers, Data collectors, Outcome adjudicators, Data analysts	Yes	
3776	NEST	Parallel	Paediatric Intensive Care Unit, Neonatal Intensive Care Unit	No		No	Individual assessment
2502	P3MC	Parallel	Outpatient clinic	Yes	Patients,	No	Patient diaries designed for the trial

					Health care providers		
2313	POP Study	Parallel	Outpatient clinic, Paediatric ward	Yes	Patients, Health care providers, Data collectors, Outcome adjudicators, Data analysts	No	DEXA scans
8483	Salford Bright Smiles Baby Study	Parallel	General practice, community clinic, Sure Start Children's Centres and other relevant community venues	No		No	Dental Assessment at 3 years of age
6906	SCAMP	Information on study characteristics not available, no response from CI					
4168	StePS	Parallel	Paediatric Intensive Care Unit	No		No	electronic CRF
4050	SWET	Parallel	Outpatient clinic	Yes	Health care providers, Data collectors, Outcome adjudicators, Data analysts	No	Blinded nurse assessment using eczema score
13601	The first BCVC nasal flu vaccine study	Other- RCT	Other-nurseries	Yes	Data analysts	No	Lab analysis of samples collected in the study
3838	TIPIT	Parallel	Neonatal Intensive Care Unit	Yes	Patients, Health care providers, Data collectors, Outcome adjudicators, Data analysts	No	Width of subarachnoid space measured by cranial ultrasound
4417	Treatments for Childhood Crohn's Disease	Parallel	Outpatient clinic	No		Yes	
8869	Wheeze and Intermittent Treatment: WAIT	Parallel	Outpatient clinic, Paediatric Ward Children's Accident & Emergency,	Yes	Patients, Health care providers, Data collectors, Outcome adjudicators,	Yes	

			Accident & Emergency Department, Paediatric Intensive Care Unit, general practice		Data analysts		
6625	A Pilot Study to Explore the Feasibility of Computerised CBT for Children	Parallel	Community clinic	Yes	Patients, Data collectors, Data analysts	No	Assessment interview with one of the research staff
6525	AIRS	Parallel	General practice	No		No	Otosocopy and tympanometry performed by the pratice nurse.
6030	Atomoxetine HSEN	Parallel	Outpatient clinic	No		Yes	
7861	Baby wipes trial	Parallel	Postnatal Ward	Yes	Data collectors, Data analysts	No	Primary outcome was skin hydration, measured using a non-invasive Corneometer on skin surface of buttocks. Baseline measurement in hospital, follow-up measurement in the home.
11874	CHAFFINCH Trial Pilot	Factorial	Paediatric Ward	No		Yes	
10428	CLICK-EAST: The Edinburgh Autism Social-attention Trial	Other-Wait-list control	Outpatient clinic, Community clinic	Yes	Data collectors, Outcome adjudicators, Data analysts	No	Video recording and coding of observation of parent-child free play session in assessment lab
9348	Dolphin Study 1	Parallel	Neonatal Intensive Care Unit, Community clinic	Yes	Patients, Health care providers, Data collectors	No	Performance on the cognitive scale of the Bayley Scales of Infant and Toddler Development III at 24 months
6797	Dolphin Study 2	Parallel	Community clinic	Yes	Patients, Health care providers,	No	Performance on the cognitive scale of the Bayley Scales of Infant and

					Data collectors		Toddler Development III at 24 months
5286	Evaluation of Telephone Administered CBT for Young People with OCD	Factorial	Outpatient clinic	Yes	Outcome adjudicators	No	clinician interview
9666	i-BASIS	Parallel	Outpatient clinic, Community clinic	Yes	Data collectors, Outcome adjudicators, Data analysts	No	videotape analysis
5863	IMPACT	Information on study characteristics not available, no response from CI					
8624	Intervention for Parents with Young Asthmatic Children						
4227	Kneeblock Study	Parallel	Other- wheelchair services	No		No	Radiograph every 12 months
5823	LEAP Study	Parallel	Paediatric Ward	No		No	Double-blind, placebo-controlled food challenge (DBPCFC), Skin Prick Test (SPT) and specific IgE at final study visit
6532	NIRS	Crossover	Neonatal Intensive Care Unit	No		No	Direct observation of FiO2 required to maintain SaO2 92%+
6251	Nitric Oxide Levels	Parallel	Outpatient clinic	Yes	Patients, Health care providers, Data collectors, Outcome adjudicators	No	CRF
8163	Optigrow Infant Feeding Study	Parallel	Other- The trial was largely conducted via home visits.	Yes	Patients, Health care providers, Data collectors, Outcome adjudicators, Data analysts	No	Nurses conducted anthropometry at home
2165	PACT	Parallel	Outpatient clinic,	Yes	Data collectors,	No	Research assessments

			Community clinic, The National Autistic Society Self(parent)-referral		Outcome adjudicators, Data analysts		(interviews/questionnaires with parents and assessments/ observations with children)
9967	Pilot RCT comparing Surgery to Observation for Intermittent Exotropia	Other- Pilot	Outpatient clinic	Yes	Outcome adjudicators	No	CRFs input into symphony database
11078	Preventing asthma exacerbations by avoiding mite allergen	Parallel	Paediatric Ward Children's Accident & Emergency Accident & Emergency Department	Yes	Patients, Health care providers, Data collectors, Outcome adjudicators	No	Parental recall
6817	STATbiTR	Parallel	School	Yes	Data collectors, Data analysts	No	A paediatric physiotherapist blinded to the allocation of groups performed the assessments in the schools.
7993	Study of Tolerance to Oral Peanut	Crossover	Outpatient clinic	No		No	Paper CRF of double-blinded food challenge
8133	Telephone consultations for children with inflammatory bowel disease	Information on study characteristics not available, no response from CI					
10090	Use of sensory blankets for children with autistic spectrum disorder	Crossover	Outpatient clinic, School, Contacting help groups	Yes	Patients, Outcome adjudicators	No	Actigraphy

Appendix 16: Classification of studies included in the NIHR portfolio review

Study ID	Study Title	Intervention	IMP/non-IMP	Disease/condition under study	Acute/Chronic/Healthy
2312	ADEPT	Timing of enteral feeding, day 2 vs. day 6	non IMP	Necrotising Enterocoloitis (NEC)	Acute
3217	Amitriptyline in EB Pain	Amitriptyline	IMP	Epidermolysis Bullosa	Chronic
12221	An alternative booster vaccine against meningitis and ear infections	Vaccine	IMP	Healthy infants	Healthy
2231	BOOST II UK	Level of arterial oxygen saturation levels	non IMP	Prematurity	Chronic
11354	Bronchiolitis of Infancy Discharge Study (BIDS)	Level of arterial oxygen saturation for stopping therapeutic oxygen	Non IMP	Bronchiolitis	Acute
8976	Can we Reduce the Number of Vaccine Injections for Children?	Vaccine	IMP	Healthy infants	Healthy
5799	CASG112	Valganciclovir	IMP	Congenital Cytomegalovirus (CMV)	Chronic
7976	CATCH	Heparin bonded or antibiotic impregnated central venous catheters (CVCs)	IMP	Paediatric Intensive Care Unit admissions needing central venous catheters for at least three days	Acute
3218	CHIP Trial	Tight Glucose control	non IMP	Intensive care treatment with an arterial line in-situ and receiving both mechanical ventilation and vasoactive support drugs following injury, major surgery or in association with critical illness in whom it is anticipated such treatment will be required to continue	Acute

				for at least 12 hours.	
9111	Cognative GA Study - TIVA versus volatile anaesthesia in children: cognitive effects	Anaesthesia: intravenous vs. volatile	IMP	Day stay general anaesthetic (GA) for multiple dental extractions and restorations	Acute
4171	DECIDE	Diabetes treatment started at home vs. hospital	non IMP	Type I Diabetes	Chronic
3777	DRN067 (FACTS)	Enhanced family communication	non IMP	Type I Diabetes	Chronic
7464	H1N1	Vaccine	IMP	Healthy infants	Healthy
7552	I2S2	Iodine supplementation vs. Placebo	IMP	Extreme prematurity	Chronic
8814	INDIGO - Pump versus MDI insulin and hypoglycaemia in children.	Multiple injections versus pump insulin therapy	IMP	Diabetes	Chronic
7553	KONCERT (PENTA18)	Lopinavir/Ritonavir	IMP	HIV	Chronic
2276	MAGNETIC	Magnesium	IMP	Acute exacerbation asthma	Acute
3774	MASCOT	Salmetrol/Monteleukast	IMP	Asthma	Chronic
2736	MCRN000 (MEE103219)	Mepolizumab	IMP	Eosinophilic esophagitis	Chronic
3297	MCRN002 (6096A1-007)	13-valent pneumococcal conjugate (13vPnC) vaccine	IMP	Healthy infants	Healthy
3826	MCRN003 (MK0954-326)	Losartan	IMP	Proteinuria in paediatric patients with or without hematuria	Chronic
4108	MCRN008 (A6281287)	genotropin	IMP	children born SGA	Chronic
4497	MCRN011 (WA18221)	tocilizumab	IMP	s JIA	Chronic
4615	MCRN014 (M06-806)	Adalimumab	IMP	Crohns Disease	Chronic
5716	MCRN017 (A6111137)	latanoprost opthalmic solution	IMP	paediatric glaucoma	Chronic
4739	MCRN018 (E2090-E044-312)	zonisamide	IMP	partial onset seizures	Chronic
5788	MCRN020 (MI-CP178)	vaccine	IMP	healthy infants	Healthy
5831	MCRN023 (V72P12)	vaccines	IMP	Healthy infants	Healthy
5858	MCRN024 (SPD489-325)	Lisdexamfetamine Dimesylate	IMP	ADHD	Chronic
5906	MCRN026 (0954_337-01)	MK-0954/Losartan Potassium	IMP	Hypertension	Chronic
6308	MCRN033 (111709)	vaccine	IMP	healthy infants	Healthy
6310	MCRN042 (SCO/BIA-2093-305)	Eslicarbazepine acetate	IMP	refractory partial seizures	Chronic

7050	MCRN049 (WA19977A)	Tocilizumab	IMP	Active Polyarticular-Course Juvenile Idiopathic Arthritis	Chronic
7122	MCRN052 (MAB-N007)	Pagibaximab Injection	IMP	Staphylococcal Sepsis	Acute
7357	MCRN057 (GT-21)	Grazax	IMP	grass pollen allergy	Chronic
7768	MCRN067 (CACZ885G2301)	Canakinumab	IMP	Systemic Juvenile Idiopathic Arthritis	Chronic
7816	MCRN071 (082-00)	Rizatriptan	IMP	Acute Treatment of Migraine	Acute
7985	MCRN076 (NN8630-1824)	Pegylated GH	IMP	Growth Hormone deficiency	Chronic
8309	MCRN084 (VX08-770-103)	VX-770	IMP	CF	Chronic
8526	MCRN089 (111763)	vaccine	IMP	healthy infants	Healthy
9513	MCRN105 (AI463-189)	Entecavir	IMP	Chronic Hepatitis B virus infection	Chronic
10290	MCRN112 (SPD503-315)	Guanfacine Hydrochloride	IMP	ADHD	Chronic
9998	MCRN119 (HGT-HIT-045)	Idursulfase	IMP	Hunter Syndrome	Chronic
10291	MCRN128 (CL2-16257-090)	Ivabradine	IMP	Dilated cardiomyopathy and chronic heart failure	Chronic
10292	MCRN129 (M0001-C303)	Prucalopride	IMP	functional constipation	Chronic
10907	MCRN142 (CNTO1275PSO3006)	Ustekinumab	IMP	psoriasis	Chronic
10909	MCRN144 (115345)	Influenza vaccine	IMP	Healthy infants	Healthy
11222	MCRN153 (NN1250-3561)	Insulin degludec	IMP	Type I DM	Chronic
11587	MCRN164 (PRI01C)	vaccine	IMP	healthy infants	Healthy
11860	MCRN171 (TRA115450)	Eltrombopag	IMP	Chronic ITP	Chronic
2258	MENDS	melatonin	IMP	children with neurodevelopmental disorders and impaired sleep	Chronic
6739	MIGS	Glutamine	IMP	Infants requiring PN and surgery for congenital or acquired gastrointestinal anomalies- gastroschisis, NEC, bowel atresia or intestinal surgery for other reasons	Acute
10727	NCRN308 - Aprepitant in paediatric CINV	Aprepitant	IMP	Chemotherapy induced nausea and vomiting	Chronic
2522	NEPHROTIC SYNDROME	Prednisolone	IMP	childhood nephrotic syndrome	Chronic
3776	NEST	cooling	non IMP	neonates with cardiorespiratory failure	Acute

2502	P3MC	Propanolol and pizotifen	IMP	Migraine	Chronic
2313	POP Study	Risedronate	IMP	Rheumatic disease	Chronic
8483	Salford Bright Smiles Baby Study	flouride varnish and behavioural intervention	IMP	healthy children	Healthy
6906	SCAMP	scNPNmax	IMP	Prematurity	Acute
4168	StePS	corticosteroids	IMP	severe sepsis	Acute
4050	SWET	ion-exchange water softener	NonIMP	eczema	Chronic
13601	The first BCVC nasal flu vaccine study	vaccine	IMP	healthy infants	Healthy
3838	TIPIT	Thyroxine	IMP	Prematurity	Chronic
4417	Treatments for Childhood Crohn's Disease	Liquid diet therapy vs. corticosteroids	IMP	Crohns Disease	Chronic
8869	Wheeze and Intermittent Treatment: WAIT	monteleukast	IMP	wheeze	Acute
6625	A Pilot Study to Explore the Feasibility of Computerised CBT for Children	cognitive behaviour therapy	nonIMP	Emotional disorders	Chronic
6525	AIRS	autoinflation	nonIMP	Otitis media with effusion	Chronic
6030	Atomoxetine HSEN	Atomoxetine	IMP	ADHD	Chronic
7861	Baby wipes trial	Cleansing system in baby wipes: non-ionic sugar derived surfactants-coco-glucoside, lauryl glucoside; emollients- glycerine and glyceryl oleate, citric acid in a rayon viscose and polyester nonwoven fibre blend	IMP	Atopic eczema/atopic dermatitis	Chronic
11874	CHAFFINCH Trial Pilot	fresh fruit	non-IMP	asthma	Chronic
10428	CLICK-EAST: The Edinburgh Autism Social-attention Trial	computer-based learning programme	non-IMP	autistic spectrum disorder	Chronic
9348	Dolphin Study 1	neurotrophic supplement containing docosahexanoic acid (DHA), uridine monophosphate (ump) and choline along with supportive	IMP	neurodisabilities in neonates	Chronic

		minerals and vitamins			
6797	Dolphin Study 2	neurotrophic supplement containing docosahexanoic acid (DHA), uridine monophosphate (ump) and choline along with supportive minerals and vitamins	IMP	CP	Chronic
5286	Evaluation of Telephone Administered CBT for Young People with OCD	telephonic vs. face to face cognitive behaviour therapy	non IMP	OCD	Chronic
9666	i-BASIS	structured psychosocial parent-mediated intervention	nonIMP	Autistic spectrum disorder (ASD)	Chronic
5863	IMPACT	Brief psychodynamic therapy (BPP), cognitive behavioural therapy (CBT) and active clinical care (ACC)	non IMP	Moderate to severe depression	
8624	Intervention for Parents with Young Asthmatic Children	Group delivered Triple P parenting seminars and telephone support	nonIMP	Asthma	Chronic
4227	Kneeblock Study	kneeblock and sacral pad	non IMP	Cerebral Palsy	Chronic
5823	LEAP Study	Peanut	non IMP	Peanut allergy/food hypersensitivity	Chronic
6532	NIRS	CPAP vs. SiPAP	non IMP	preterm neonates with lung disease needing respiratory support	Acute
6251	Nitric Oxide Levels	monitoring exhaled Nitric oxide levels	non IMP	Asthma	Chronic
8163	Optigrow Infant Feeding Study	milk formula	non IMP	healthy infants	Healthy
2165	PACT	trial communication intervention	non IMP	autistic spectrum disorder	Chronic
9967	Pilot RCT comparing Surgery to Observation for Intermittent Exotropia	surgery vs. active monitoring	non IMP	Intermittent exotropia	Chronic
11078	Preventing asthma exacerbations by avoiding mite allergen	Mite proof bedding	nonIMP	Asthma	Chronic
6817	STATbiTR	exercise programs	non IMP	CP	Chronic

7993	Study of Tolerance to Oral Peanut	peanut oral immunotherapy with peanut protein	IMP	peanut allergy	Chronic
8133	Telephone consultations for children with inflammatory bowel disease	telephonic vs. face to face consultation	non IMP	IBD	Chronic
10090	Use of sensory blankets for children with autistic spectrum disorder	sensory weighted blankets	non IMP	ASD	Chronic

Appendix 17: Recruitment survey questionnaire tool (Chapter 4)

1. Please enter your ID number

_____

2. Please indicate your role with regards to recruitment to the trial
[ ] Site lead/PI
[ ] Medical practitioner
[ ] Research nurse
[ ] Other

Please describe your role in relation to recruitment to the trial

_____

3. Which site/hospital were you recruiting from?

_____

4. Have you been involved for the whole trial period?
[ ] Yes
[ ] No

Was this during
[ ] setup/early recruitment period
[ ] once trial established at site

How long were you involved in recruiting for the trial? (approximately, in months)

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5. Trial level factors affecting recruitment
Listed below are *trial level factors* that commonly affect recruitment. Please indicate whether a listed factor was a facilitator or barrier to recruitment to the trial and rate them from -3 to +3 as below:
-3 strong barrier
-2 intermediate barrier
-1 weak barrier
0 not applicable
+1 weak facilitator
+2 intermediate facilitator
+3 strong facilitator

Factors	-3	-2	-1	0	+1	+2	+3
Funding							
Trial design							
Patient inclusion criteria							
Being a drug trial							
Study protocol compared to clinical practice							
Clinical equipoise							
Previous feasibility assessment							
Previous pilot trial							
Publicity by the trial team							
External publicity							
Trial management							
Protocol amendments							
Seasonal variation							

6. Site level factors affecting recruitment

Listed below are *site level factors* that commonly affect recruitment. Please indicate whether a listed factor was a facilitator or barrier to recruitment to the trial and rate them from -3 to +3 as below:

-3 strong barrier
-2 intermediate barrier
-1 weak barrier
0 not applicable
+1 weak facilitator
+2 intermediate facilitator
+3 strong facilitator

Factors	-3	-2	-1	0	+1	+2	+3
Time to open up site							
Recruitment target							
Time to complete administrative work related to the trial							
Number of trained staff							
Local clinical arrangements							
Choice of recruitment setting							
GCP training							
Data collection process							
Competing local research projects							
Local research culture							

7. Patient level factors affecting recruitment

Listed below are *patient level factors* that commonly affect recruitment. Please indicate whether a listed factor was a facilitator or barrier to recruitment to the trial and rate them from -3 to +3 as below:

-3 strong barrier
-2 intermediate barrier
-1 weak barrier
0 not applicable
+1 weak facilitator
+2 intermediate facilitator
+3 strong facilitator

Factors	-3	-2	-1	0	+1	+2	+3
Consent rate							
Familiarity with experimental treatment							
Patients'/parents' attitude towards their taking experimental medicine or placebo							
Patients'/parents' preference for a particular treatment							
Patients'/parents' concerns about side effects of new drug							
Duration of trial and follow up							
Treatment choice by random allocation							
Additional trial investigations							
Additional travel and extra costs							
Intervention available only in the trial							
Communication between research team and patient/parents							
Clinician influence							
Language or cultural barriers							

8. Clinical Team factors affecting recruitment

Listed below are *clinical team factors* that commonly affect recruitment. Please indicate whether a listed factor was a facilitator or barrier to recruitment to the trial and rate them

from -3 to +3 as below:
-3 strong barrier
-2 intermediate barrier
-1 weak barrier
0 not applicable
+1 weak facilitator
+2 intermediate facilitator
+3 strong facilitator

Factors	-3	-2	-1	0	+1	+2	+3
Research experience of clinical team							
Presence of designated research nurse/practitioner							
Availability of designated research team							
Availability of research staff out of hours							
Shift patterns of work							
Motivation of clinical team							
Clinical workload							
Perceived importance of research generally in clinical practice							
Perceived importance of the particular research question							
Communication skills of clinical team							
Clinician preference for particular treatment							
Clinician attitude to involving patients in research							
Difficulty in approaching patients for consent							

9. Information and consent related factors affecting recruitment
Listed below are *information ad consent related factors* that commonly affect recruitment. Please indicate whether a listed factor was a facilitator or barrier to recruitment to the trial and rate them from -3 to +3 as below:
-3 strong barrier
-2 intermediate barrier
-1 weak barrier
0 not applicable
+1 weak facilitator
+2 intermediate facilitator
+3 strong facilitator

Factors	-3	-2	-1	0	+1	+2	+3
Amount and complexity of trial information provided							
Clarity in presentation of trial information							
Social and emotional dynamics of trial discussion							
Time and setting of consent seeking							
Senior doctors and nurses seeking consent							
Experience and training of clinical team seeking consent							

10. Study team factors affecting recruitment

Listed below are *study team factors* that commonly affect recruitment. Please indicate whether a listed factor was a facilitator or barrier to recruitment to the trial and rate them from -3 to +3 as below:
-3 strong barrier
-2 intermediate barrier
-1 weak barrier
0 not applicable
+1 weak facilitator
+2 intermediate facilitator
+3 strong facilitator

Factors	-3	-2	-1	0	+1	+2	+3
Motivation of the study team at site							
Communication and coordination between study team members at site							
Communication and coordination between study team at site and CTU							
Research experience of PI and study team members at site							

11. What interventions or strategies were applied to overcome any hurdles identified in previous questions and how effective were these?

12. How would you organise the trial differently to improve recruitment? Please include additional comments, if any

Appendix 18: MAGNETIC trial sites (Chapter 5)

SN	Hospital sites
	Sites that recruited
1	St Thomas Hospital
2	Royal Devon and Exeter Hospital
3	Derbyshire Children's Hospital
4	Tameside General Hospital
5	Leicester Royal Infirmary
6	Royal Albert Edward Infirmary, Wigan
7	Queens Hospital, Burton
8	University Hospital of Wales
9	Royal London Hospital
10	Countess of Chester Hospital
11	Macclesfield District General Hospital
12	Royal Hospital for Sick Children, Glasgow
13	Sheffield Children's Hospital
14	Preston Royal Infirmary
15	Bristol Royal Children's Hospital
16	QMC Nottingham
17	Victoria Hospital Blackpool
18	Ormskirk and District Hospital
19	Wythenshawe Hospital
20	Birmingham Children's Hospital
21	University Hospital of North Staffordshire
22	Craigavon Area Hospital
23	Birmingham Heartlands Hospital
24	Royal Aberdeen Children's Hospital
25	University Hospital North Tees
26	University Hospital Lewisham
27	Altnagelvin Area Hospital
28	Southampton General Hospital
29	Royal Manchester Children's Hospital
30	Royal Cornwall Hospital
	Sites that opened up but could not recruit
1	Leighton Hospital Crewe
2	Whiston Hospital
3	Royal Alexandra Children's Hospital Brighton
	Sites that did not open up
1	Royal Belfast Hospital for Sick Children
2	Antrim Hospital
3	Morriston Hospital, Swansea
4	Fairfield General Hospital

Appendix 19: MAGNETIC recruitment survey

1) Please enter your ID number

2) Please indicate your role with regards to recruitment to MAGNETIC

- ☐ Site lead/PI
- ☐ Medical practitioner
- ☐ Research nurse
- ☐ Other

Please describe your role in relation to recruitment to MAGNETIC

3) Which site/hospital were you recruiting from?

4) Have you been involved with MAGNETIC for the whole trial period?

- ○ Yes
- ○ No

Was this during

- ☐ setup/early recruitment period
- ☐ once trial established at site

How long were you involved in recruiting for MAGNETIC? (approximately, in months)

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5) Listed below are trial specific factors that commonly affect recruitment. Please indicate whether a listed factor was a facilitator or barrier to recruitment to MAGNETIC and rate them from -3 to +3 as below:
-3 strong barrier
-2 intermediate barrier
-1 weak barrier
0 not applicable
+1 weak facilitator
+2 intermediate facilitator
+3 strong facilitator

	-3	-2	-1	0	+1	+2	+3
Funding	○	○	○	○	○	○	○

Trial design	○	○	○	○	○	○	○
Patient inclusion criteria	○	○	○	○	○	○	○
MAGNETIC being a drug trial	○	○	○	○	○	○	○
Study protocol compared to clinical practice	○	○	○	○	○	○	○
Clinical equipoise	○	○	○	○	○	○	○
Previous feasibility assessment	○	○	○	○	○	○	○
Previous pilot trial	○	○	○	○	○	○	○
Publicity by the trial team	○	○	○	○	○	○	○
External publicity	○	○	○	○	○	○	○
Trial management	○	○	○	○	○	○	○
Protocol amendments	○	○	○	○	○	○	○
Seasonal variation	○	○	○	○	○	○	○

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6) Listed below are site specific factors that commonly affect recruitment. Please indicate whether a listed factor was a facilitator or barrier to recruitment to MAGNETIC and rate them from -3 to +3 as below:
-3 strong barrier
-2 intermediate barrier
-1 weak barrier
0 not applicable
+1 weak facilitator
+2 intermediate facilitator
+3 strong facilitator

	-3	**-2**	**-1**	**0**	**+1**	**+2**	**+3**
Time to open up site	○	○	○	○	○	○	○

Recruitment target	○	○	○	○	○	○	○
Time to complete administrative work related to the trial	○	○	○	○	○	○	○
Number of trained staff	○	○	○	○	○	○	○
Local clinical arrangements	○	○	○	○	○	○	○
Choice of recruitment setting	○	○	○	○	○	○	○
GCP training	○	○	○	○	○	○	○
Data collection process	○	○	○	○	○	○	○
Competing local research projects	○	○	○	○	○	○	○
Local research culture	○	○	○	○	○	○	○

7) Listed below are patient specific factors that commonly affect recruitment. Please indicate whether a listed factor was a facilitator or barrier to recruitment to MAGNETIC and rate them from -3 to +3 as below:
-3 strong barrier
-2 intermediate barrier
-1 weak barrier
0 not applicable
+1 weak facilitator
+2 intermediate facilitator
+3 strong facilitator

	-3	**-2**	**-1**	**0**	**+1**	**+2**	**+3**
Consent rate	○	○	○	○	○	○	○
Familiarity with experimental treatment	○	○	○	○	○	○	○
Parent's attitude towards their taking experimental medicine or placebo	○	○	○	○	○	○	○

Parent's preference for a particular treatment	○	○	○	○	○	○	○
Parent's concerns about side effects of new drug	○	○	○	○	○	○	○
Duration of trial and follow up	○	○	○	○	○	○	○
Treatment choice by random allocation	○	○	○	○	○	○	○
Additional trial investigations	○	○	○	○	○	○	○
Additional travel and extra costs	○	○	○	○	○	○	○
Intervention available only in the trial	○	○	○	○	○	○	○
Communication between research team and parents	○	○	○	○	○	○	○
Clinician influence	○	○	○	○	○	○	○
Language or cultural barriers	○	○	○	○	○	○	○

8) Listed below are clinical team factors that commonly affect recruitment. Please indicate whether a listed factor was a facilitator or barrier to recruitment to MAGNETIC and rate them from -3 to +3 as below:
-3 strong barrier
-2 intermediate barrier
-1 weak barrier
0 not applicable
+1 weak facilitator
+2 intermediate facilitator
+3 strong facilitator

	-3	**-2**	**-1**	**0**	**+1**	**+2**	**+3**
Research experience of clinical team	○	○	○	○	○	○	○
Presence of designated research nurse/practitioner	○	○	○	○	○	○	○

Availability of designated research team	○	○	○	○	○	○	○
Availability of research staff out of hours	○	○	○	○	○	○	○
Shift patterns of work	○	○	○	○	○	○	○
Motivation of clinical team	○	○	○	○	○	○	○
Clinical workload	○	○	○	○	○	○	○
Perceived importance of research generally in clinical practice	○	○	○	○	○	○	○
Perceived importance of the particular research question	○	○	○	○	○	○	○
Communication skills of clinical team	○	○	○	○	○	○	○
Clinician preference for particular treatment	○	○	○	○	○	○	○
Clinician attitude to involving patients in research	○	○	○	○	○	○	○
Difficulty in approaching patients for consent	○	○	○	○	○	○	○

9) Listed below are Information and consent related factors that commonly affect recruitment. Please indicate whether a listed factor was a facilitator or barrier to recruitment to MAGNETIC and rate them from -3 to +3 as below:
-3 strong barrier
-2 intermediate barrier
-1 weak barrier
0 not applicable
+1 weak facilitator
+2 intermediate facilitator
+3 strong facilitator

	-3	**-2**	**-1**	**0**	**+1**	**+2**	**+3**

Amount and complexity of trial information provided	○	○	○	○	○	○	○
Clarity in presentation of trial information	○	○	○	○	○	○	○
Social and emotional dynamics of trial discussion	○	○	○	○	○	○	○
Time and setting of consent seeking	○	○	○	○	○	○	○
Senior doctors and nurses seeking consent	○	○	○	○	○	○	○
Experience and training of clinical team seeking consent	○	○	○	○	○	○	○

10) Listed below are study team factors that commonly affect recruitment. Please indicate whether a listed factor was a facilitator or barrier to recruitment to MAGNETIC and rate them from -3 to +3 as below:
-3 strong barrier
-2 intermediate barrier
-1 weak barrier
0 not applicable
+1 weak facilitator
+2 intermediate facilitator
+3 strong facilitator

	-3	**-2**	**-1**	**0**	**+1**	**+2**	**+3**
Motivation of MAGNETIC study team at site	○	○	○	○	○	○	○
Communication and coordination between study team members at site	○	○	○	○	○	○	○
Communication and coordination between study team at site and CTU	○	○	○	○	○	○	○
Research experience of PI and study team members at site	○	○	○	○	○	○	○

11) What interventions or strategies were applied to overcome any hurdles identified in previous questions and how effective were these?

12) How would you organise MAGNETIC differently to improve recruitment? Please include additional comments, if any

Appendix 20: Email sent to NRES Queries Line (queries@nres.nhs.uk) on 18/07/2011

Dear NRES team

I am a Clinical PhD student in the North West Hub for Trials Methodology Research. Could I please request for advice on the following:

MAGNETIC is a randomised, multi-center, placebo controlled study of nebulised magnesium in acute severe asthma in children which has been completed in April 2011. The Chief Investigator of MAGNETIC and project team from NWHTMR wish to explore the recruitment experience of MAGNETIC study teams at sites by conducting an online survey collating views of study team members on facilitators and barriers to recruitment, effect of various recruitment strategies applied and suggestions for change in organisation of future trials such as MAGNETIC. I have attached a project summary for your consideration.

Please advise if we would require ethical clearance for this project. Having read your 'Defining Research' guidance it would seem that this survey may not be designated as research but as service evaluation of NHS RCTs, however I would be very grateful for your advice regarding my interpretation of the guidance in this regard.

I look forward to hearing from you.

Many Thanks
Geetinder

Dr Geetinder Kaur
Clinical Research Fellow
Institute of Child Health
Alder Hey Hospital
Liverpool

Response received from NRES Query line on 20/07/2011

Thank you for your further email enquiry. As you are aware, our leaflet *"Defining Research"*, explains how we differentiate research from other activities, and is published at: http://www.nres.npsa.nhs.uk/applications/is-your-project-research/.

Based on the information you provided, our advice is that the project is not considered to be research according to this guidance. It would appear to be **Service Evaluation** and therefore it does not require ethical review by a NHS Research Ethics Committee.

If you are undertaking the project within the NHS, you should check with the relevant NHS care organisation(s) what other review arrangements or sources of advice apply to projects of this type. Guidance may also be available from the clinical governance office.

Although ethical review by an NHS REC is not necessary in this case, all types of study involving human participants should be conducted in accordance with basic ethical principles, such as informed consent and respect for the confidentiality of participants. Also, in processing identifiable data there are legal requirements under the Data Protection Act 2000. When undertaking an audit or service/therapy evaluation, the investigator and his/her team are responsible for considering the ethics of their project with advice from within their organisation. University projects may require approval by the university ethics committee. Please refer to our guidance on student research at: http://www.nres.npsa.nhs.uk/applications/guidance/research-guidance/?esctl1654606_entryid62=83668.

This response should not be interpreted as giving a form of ethical approval or any endorsement to your project, but it may be provided to a journal or other body as evidence that ethical approval is not required under NHS research governance arrangements.

However, if you, your sponsor/funder or any NHS organisation feel that the project should be managed as research, and/or that ethical review by an NHS REC is essential, then please write setting out your reasons and we will be pleased to consider your request further.

Where NHS organisations have clarified that a project is not to be managed as research, the Research Governance Framework states that it should not be presented as research within the NHS.

If you have received advice on the same or a similar matter from a different source (for example directly from a Research Ethics Committee (REC) or from an NHS R&D department), it would be helpful if you could share the initial query and response received if then seeking additional advice through the NRES Queries service.

However, if you have been asked to follow a particular course of action by a REC as part of a provisional or conditional opinion, then the REC requirements are mandatory to the opinion, unless specifically revised by that REC. Should you wish to query the REC requirements, this should either be through contacting the REC direct or, alternatively, the relevant local operational manager.

Regards

Queries Line
National Research Ethics Service
National Patient Safety Agency
4-8 Maple Street
London
W1T 5HD

Appendix 21: Covering letter for survey questionnaire (Chapter 5)

Dear

Thank you for being involved in MAGNETIC. There has been a huge effort form all those involved and, as I am sure you know, we have been successful in recruiting over 500 children. Some centres managed to recruit well and other had many difficulties, some overcome and others not. We are trying to understand what went well and what didn't go so well.

We are contacting you to gather information on factors which acted as facilitators/barriers for recruitment to MAGNETIC and would be grateful if you could share your experiences with us. This information will be very useful in designing future trials and will be a part of a PhD project for Dr Geetinder Kaur who is a clinical PhD student in the North West Hub for Trials Methodology Research under the supervision of Professor Rosalind Smyth and Professor Paula Williamson.

The survey is short and will only take a few minutes to complete via the following link:

http://edu.surveygizmo.com/s3/583910/MAGNETIC-recruitment-survey

The survey questionnaire has a list of some commonly reported factors affecting recruitment and questions with free text space for additional comments. Please answer all the questions and order the factors from -3 to +3 depending on whether you think the factor acted as a facilitator (+1 to +3) or a barrier (-1 to -3) or did not affect recruitment at your site (0).

All information provided will be strictly confidential. Your personal details are not required for this survey and a unique identification number will be used instead of your name when collating responses. Please note that whilst we need to know site details for data management purposes, no site will be identified in any publication and the data will be treated in strictest confidence within the research team listed in this letter.

Many thanks
Kind Regards,
Dr Colin Powell (Chief Investigator)
John Lowe (Trial Coordinator)
Dr Geetinder Kaur (Clinical PhD student)

Appendix 22: Scatterplots: Calibrated site recruitment and PI response for factors

Trial level factors

Fig. I: Relationship between funding and calibrated site recruitment

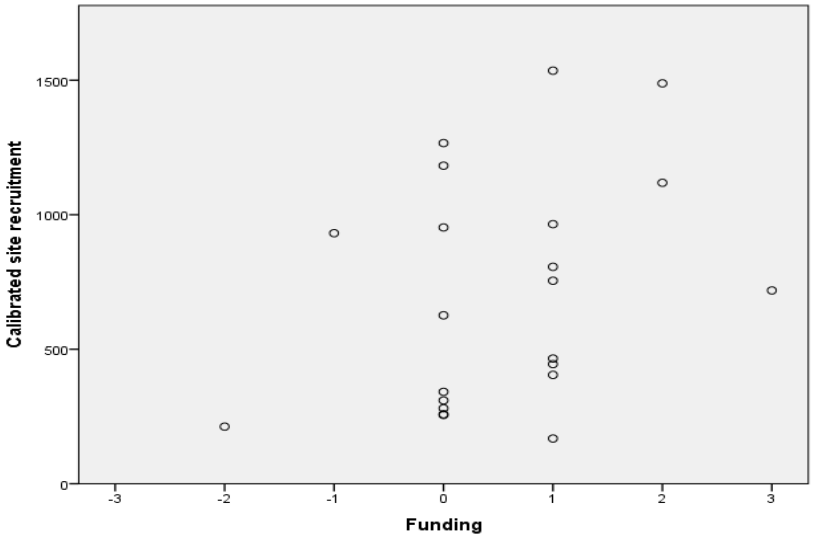


Fig. II: Relationship between trial design and calibrated site recruitment

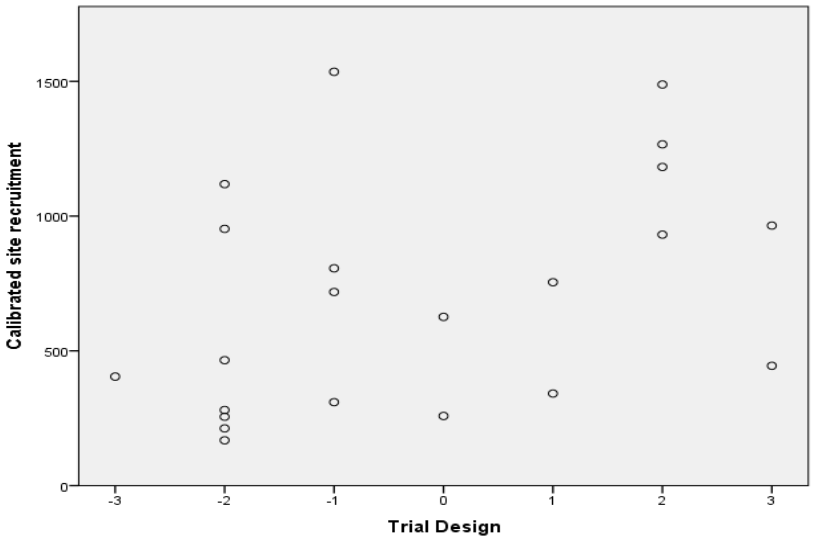


Fig. III: Relationship between patient inclusion criteria and calibrated site recruitment

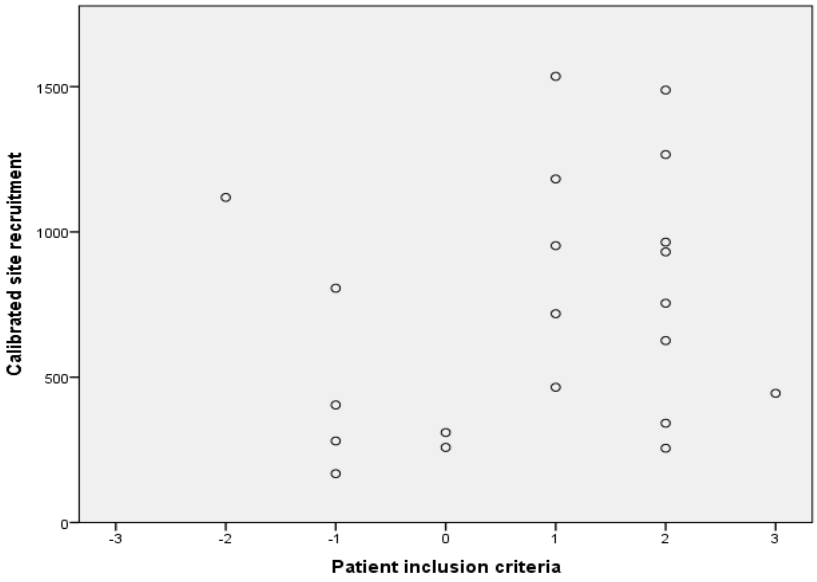


Fig. IV: Relationship between MAGNETIC being a drug trial and calibrated site recruitment

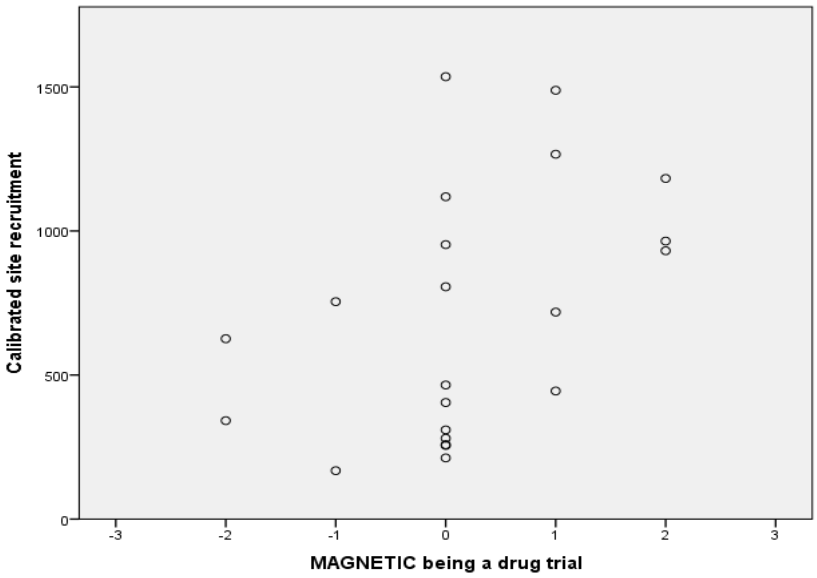


Fig. V: Relationship between study protocol compared to clinical practice and calibrated site recruitment

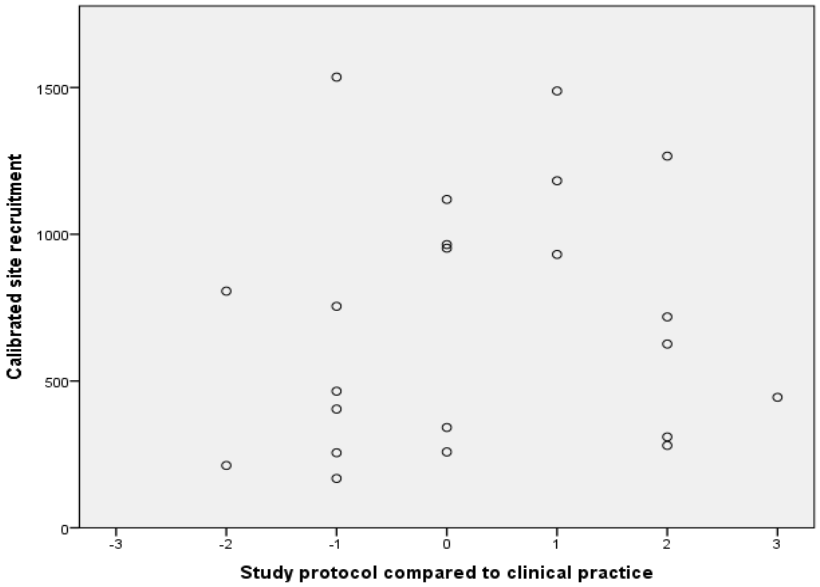


Fig. VI: Relationship between clinical equipoise and calibrated site recruitment

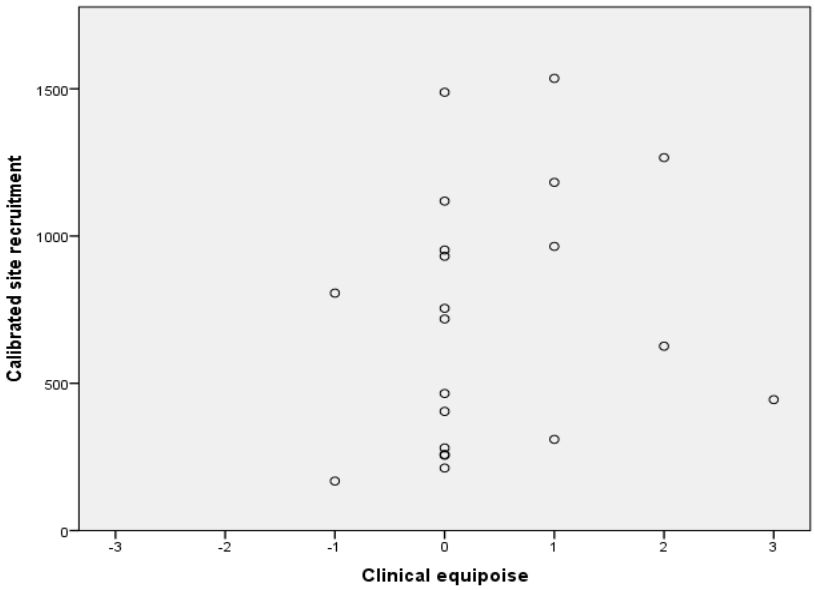


Fig. VII: Relationship between previous feasibility assessment and calibrated site recruitment

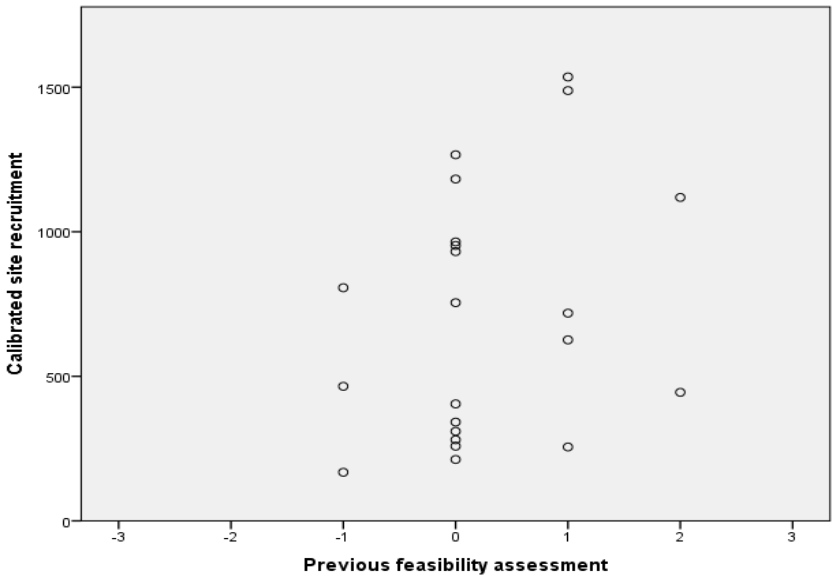


Fig. VIII: Relationship between previous pilot trial and calibrated site recruitment

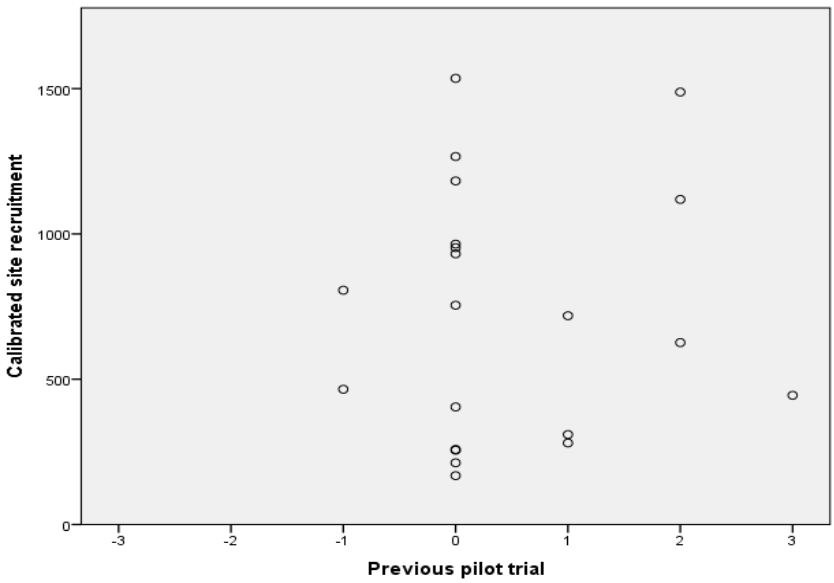


Fig. IX: Relationship between publicity by trial team and calibrated site recruitment

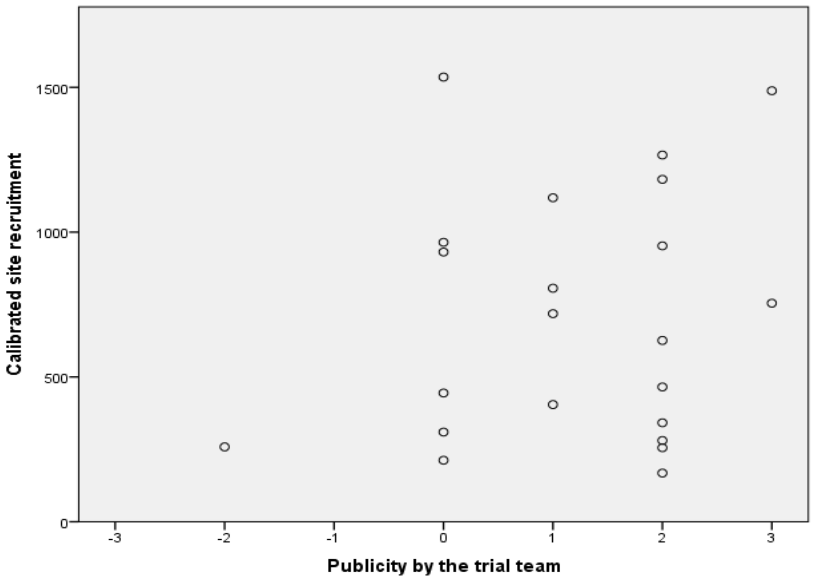


Fig. X: Relationship between external publicity and calibrated site recruitment

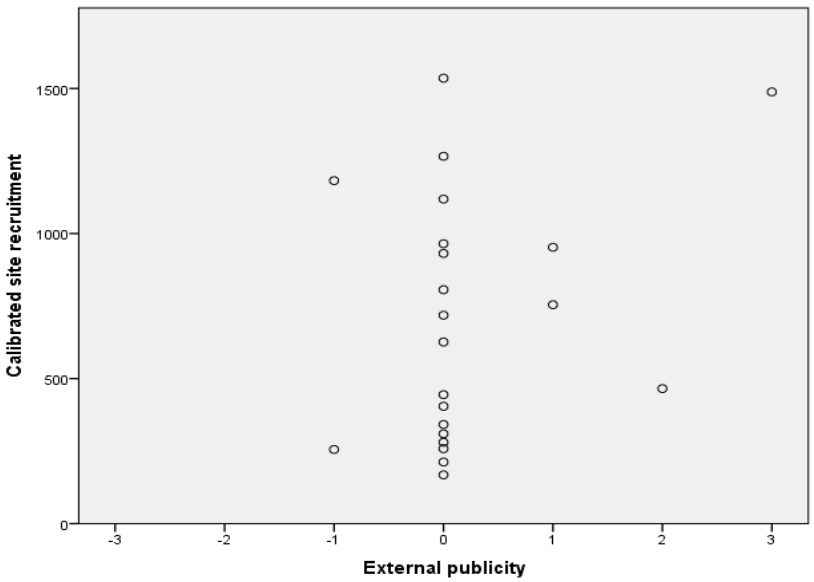


Fig. XI Relationship between trial management and calibrated site recruitment

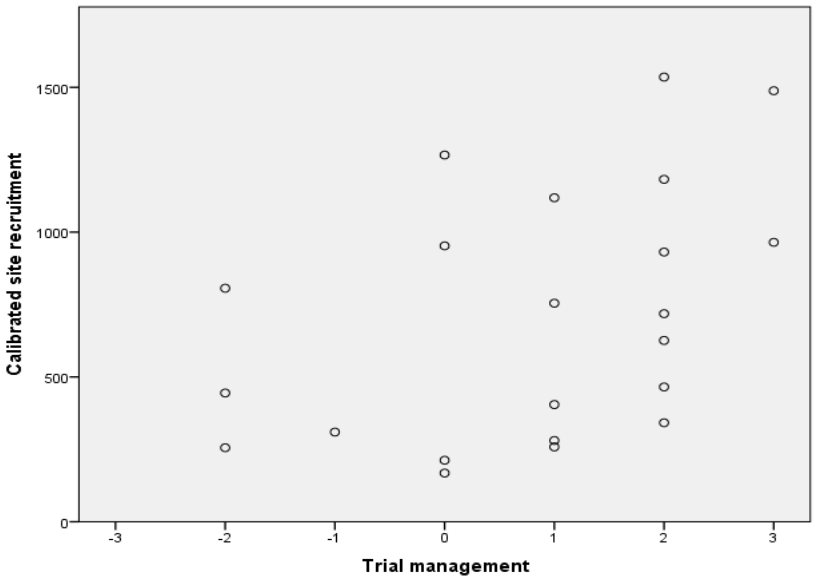


Fig. XII Relationship between trial management and calibrated site recruitment

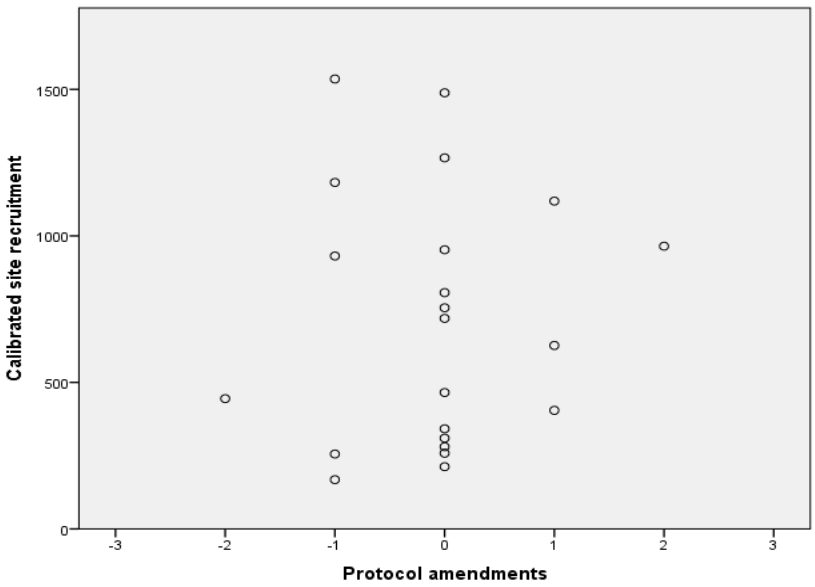
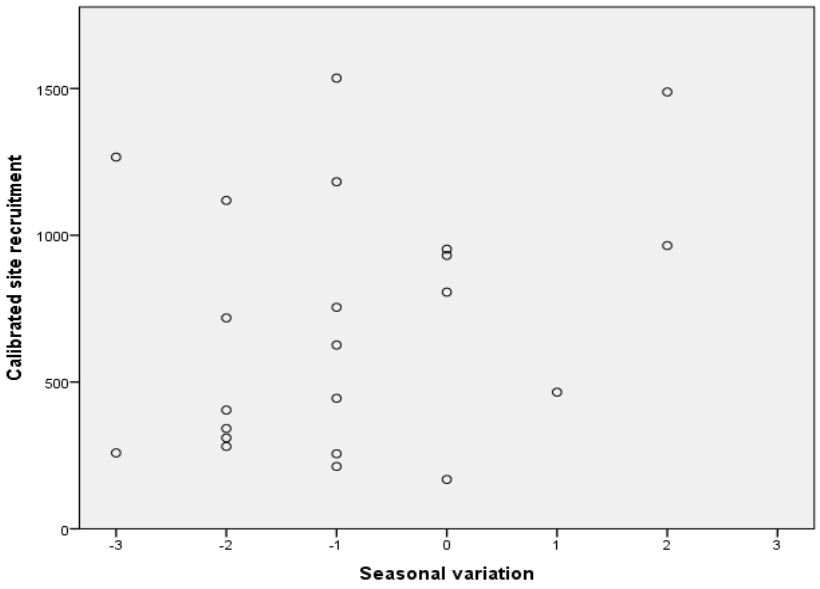


Fig. XIII Relationship between seasonal variation and calibrated site recruitment



Site level factors

Fig. XIV Relationship between time to open up site and calibrated site recruitment

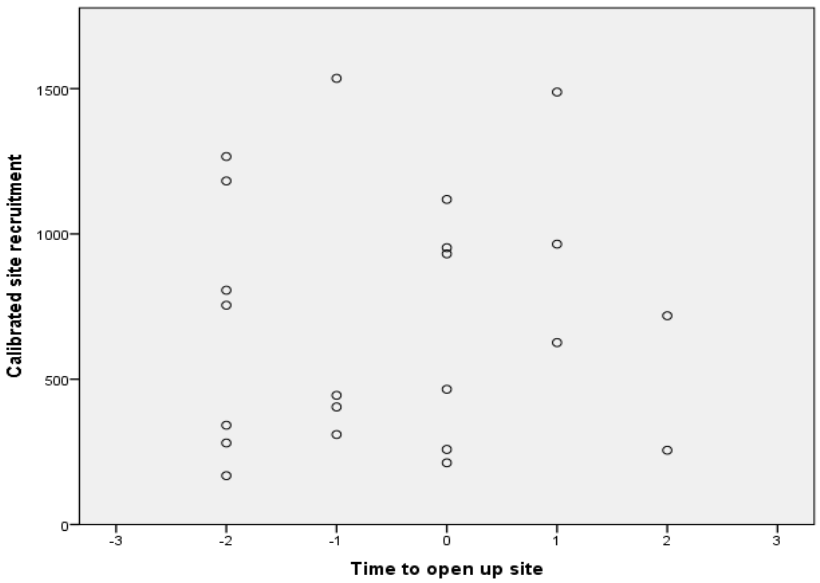


Fig. XV: Relationship between recruitment target and calibrated site recruitment

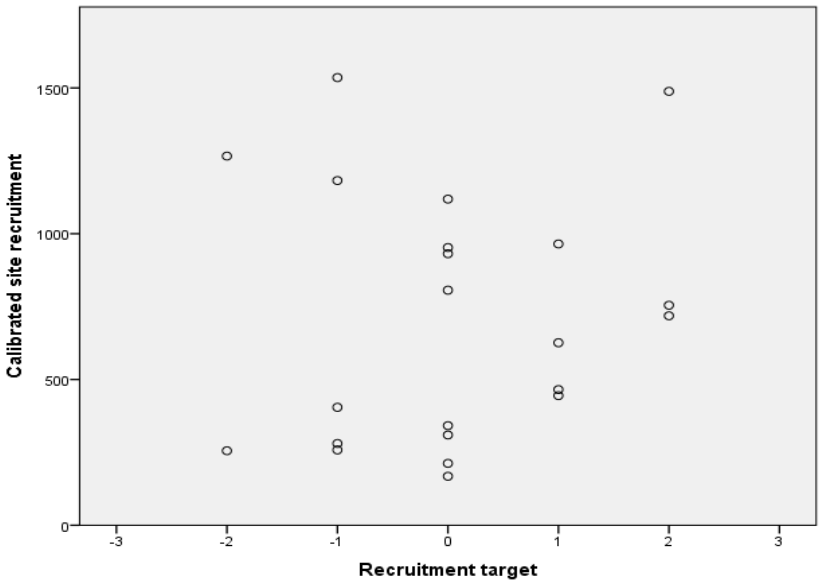


Fig. XVI: Relationship between time taken to complete trial related administrative work and calibrated site recruitment

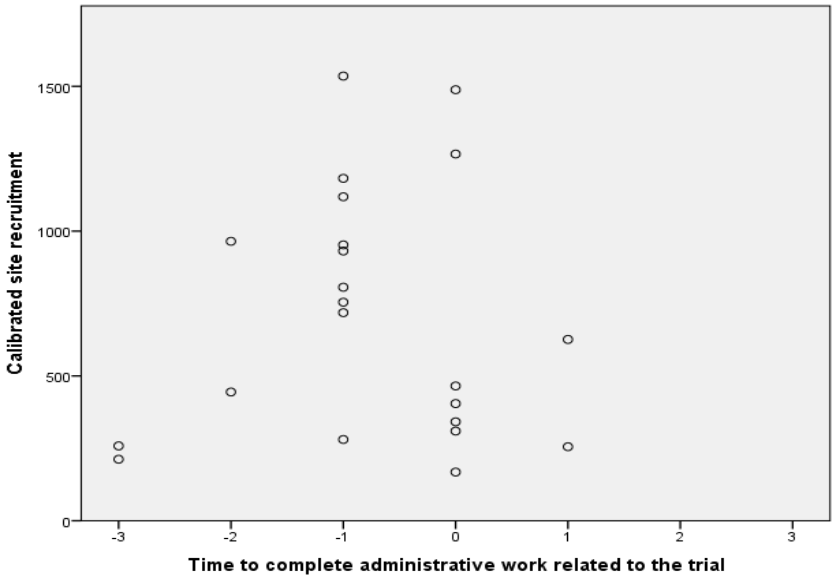


Fig. XVII: Relationship between number of trained staff and calibrated site recruitment

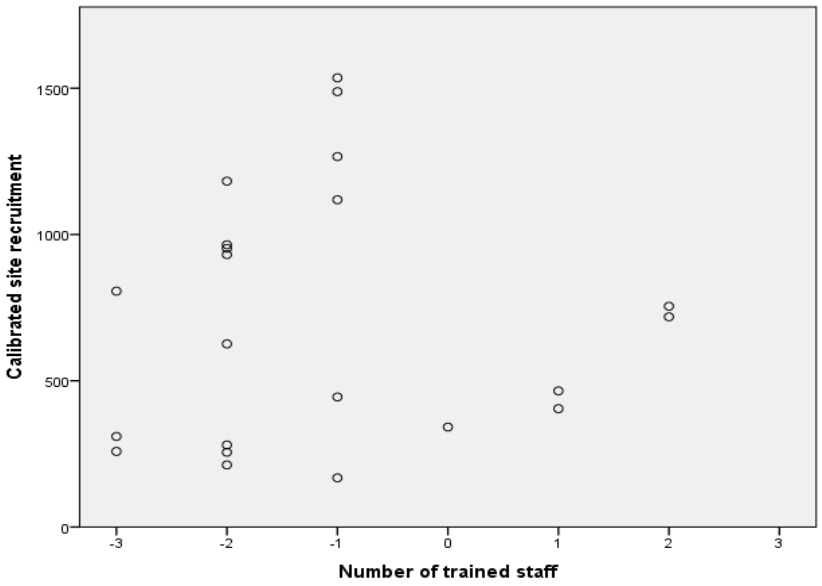


Fig. XVIII: Relationship between time taken to complete trial related administrative work and calibrated site recruitment

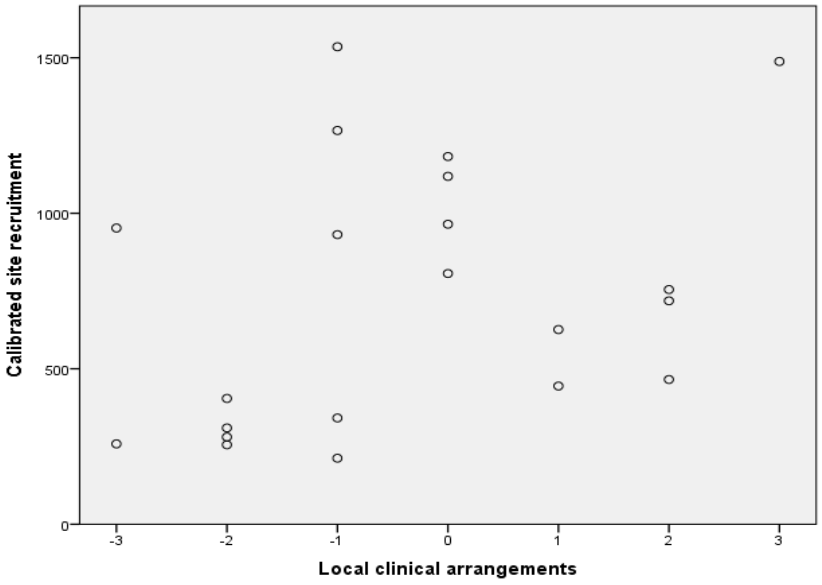


Fig. IXX: Relationship between choice of recruitment setting and calibrated site recruitment

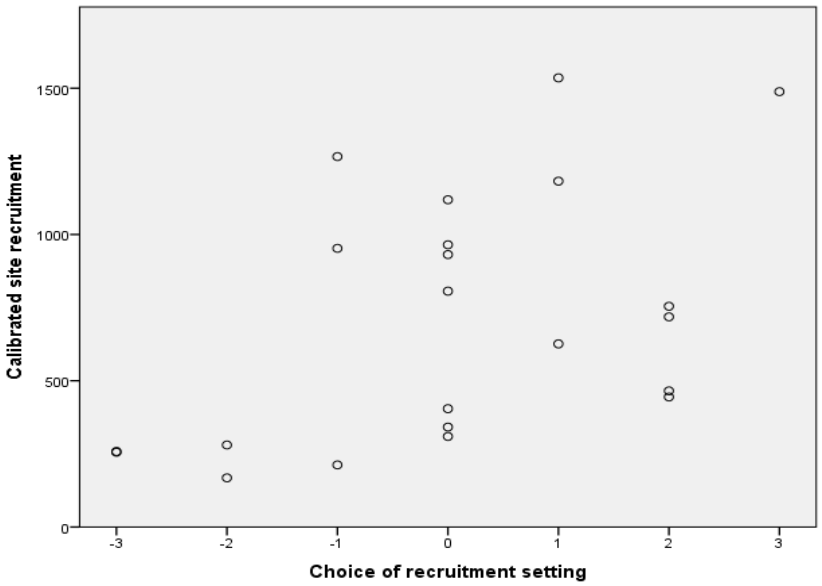


Fig. XX: Relationship between GCP training and calibrated site recruitment

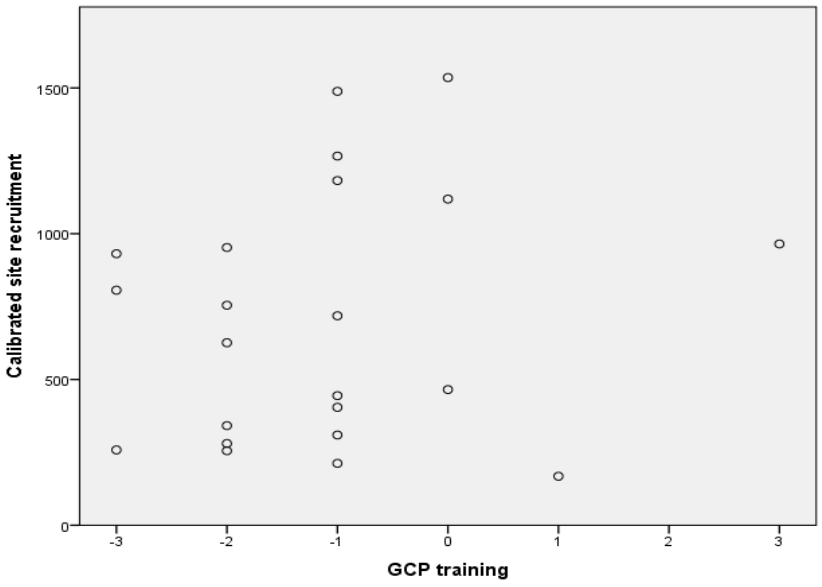


Fig. XXI: Relationship between data collection process and calibrated site recruitment

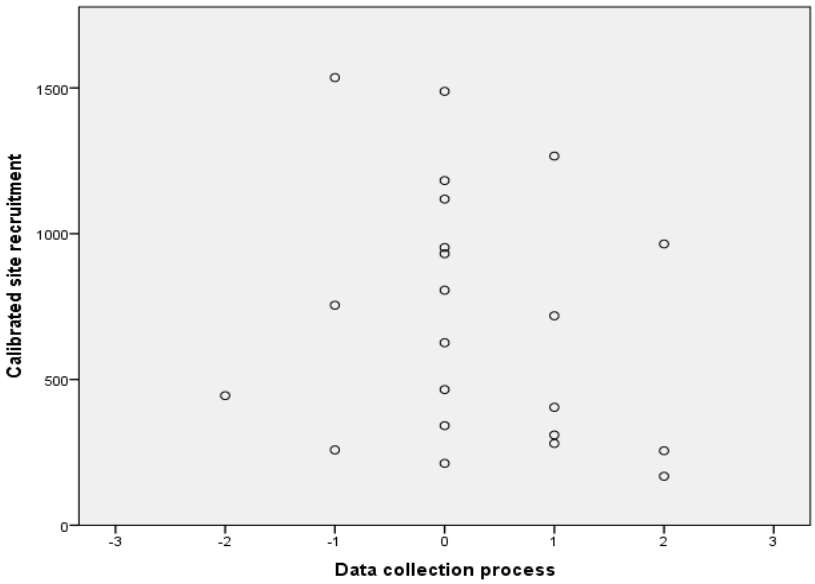


Fig. XXII: Relationship between competing local research projects and calibrated site recruitment

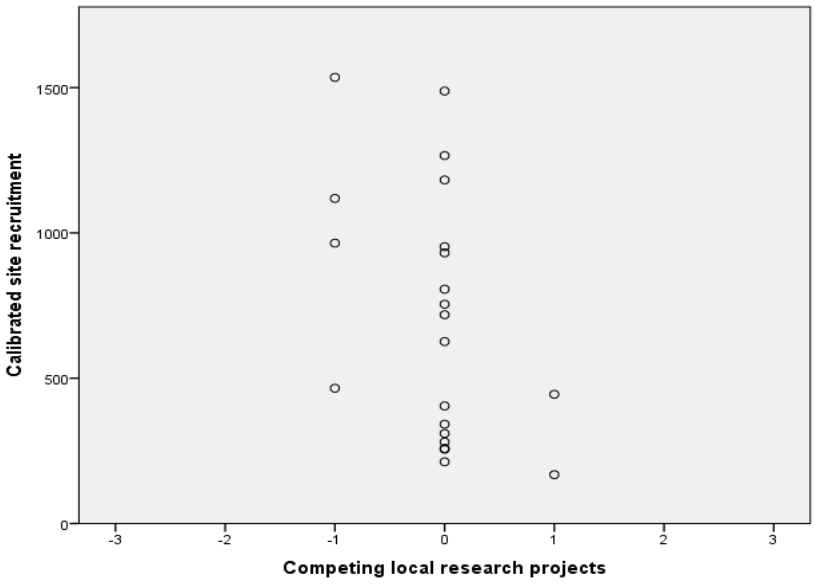
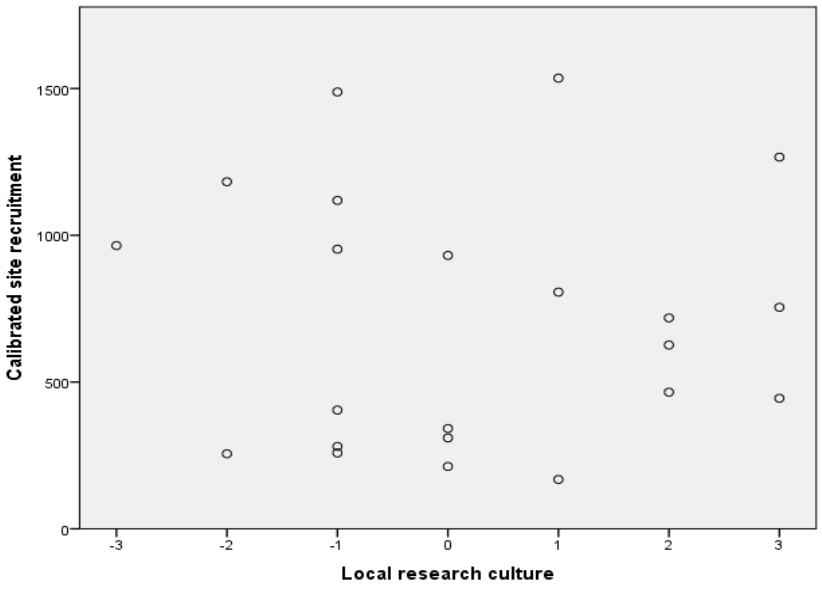


Fig. XXIII: Relationship between local research culture and calibrated site recruitment



Patient related factors

Fig. XXIV: Relationship between consent rate and calibrated site recruitment

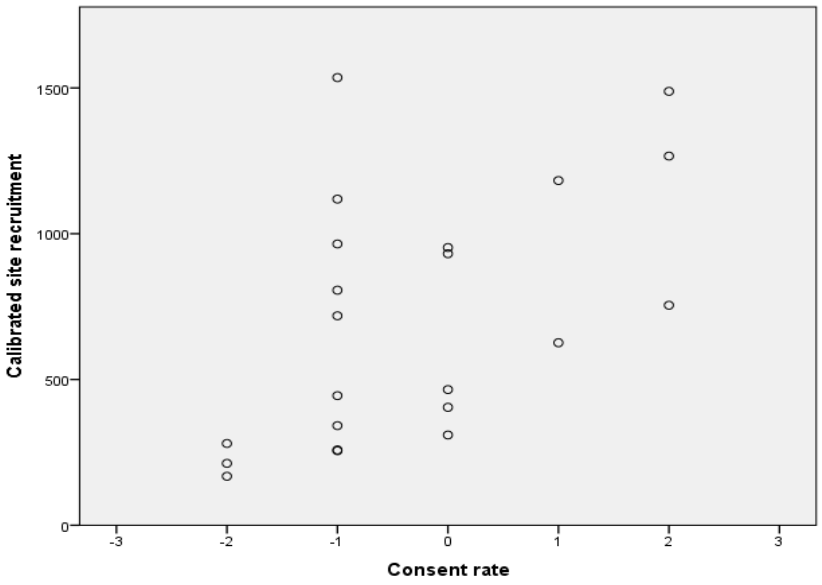


Fig. XXV: Relationship between familiarity with experimental treatment and calibrated site recruitment

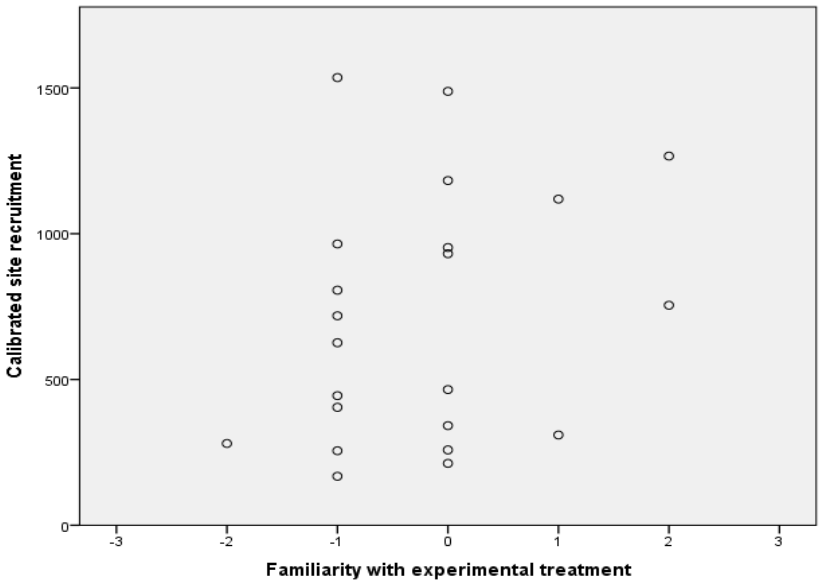


Fig. XXVI: Relationship between parents' attitude towards taking experimental medicine and calibrated site recruitment

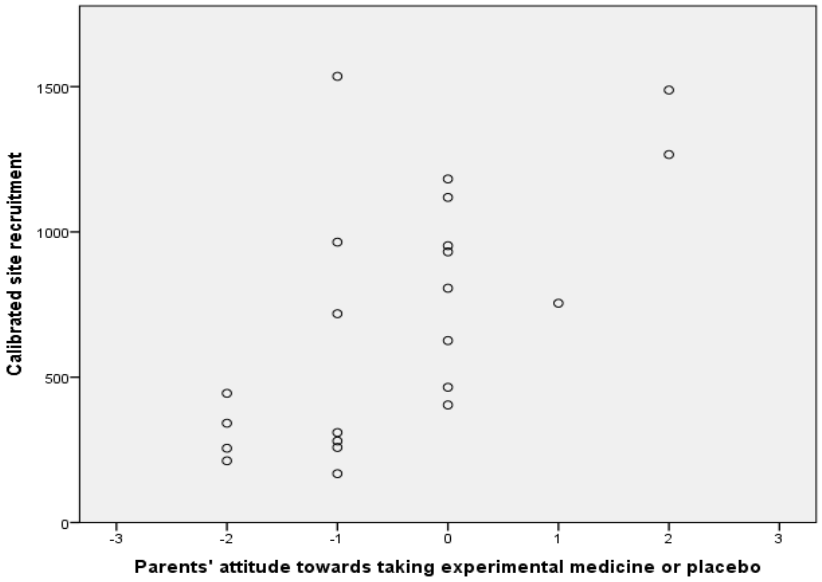


Fig. XXVII: Relationship between parents' preference for a particular treatment and calibrated site recruitment

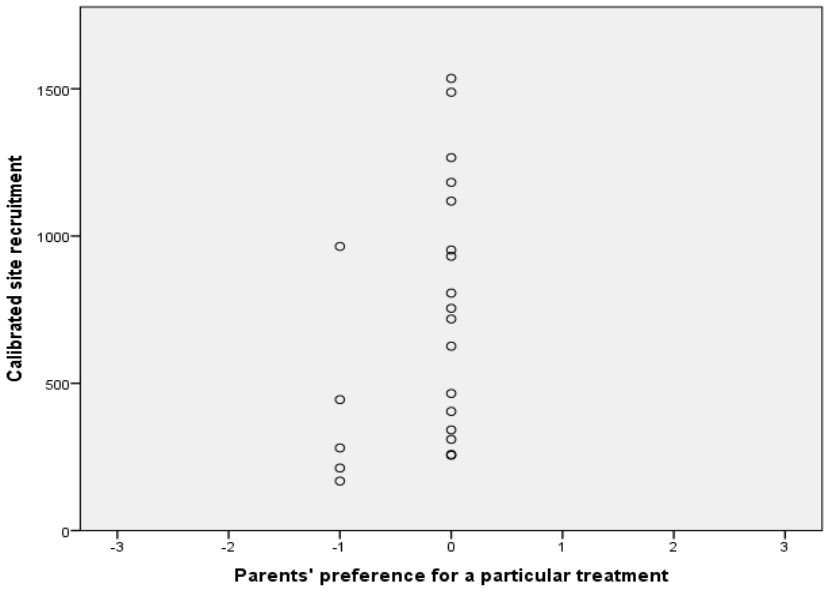


Fig. XXVIII: Relationship between parents' concerns about side effects of new drug and calibrated site recruitment

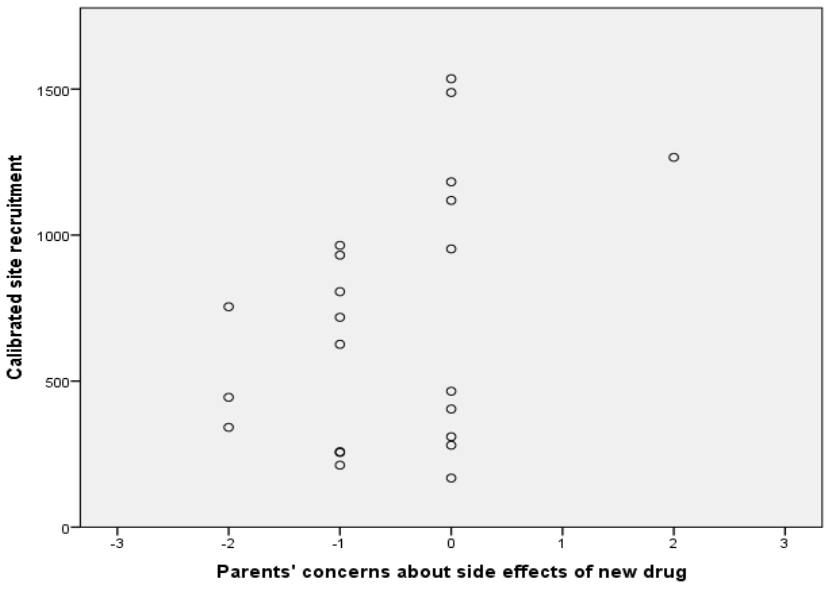


Fig.XXIX: Relationship between duration of trial and follow up and calibrated site recruitment

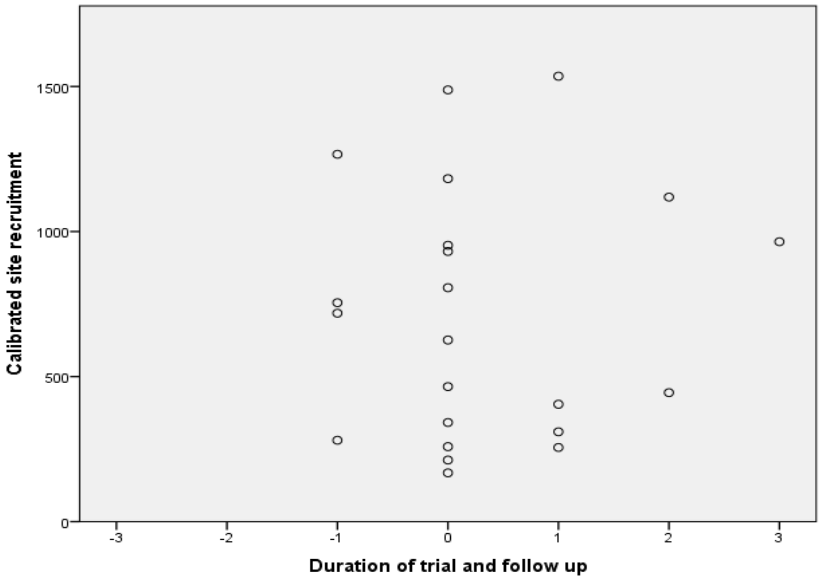


Fig. XXX: Relationship between treatment choice by random allocation and calibrated site recruitment

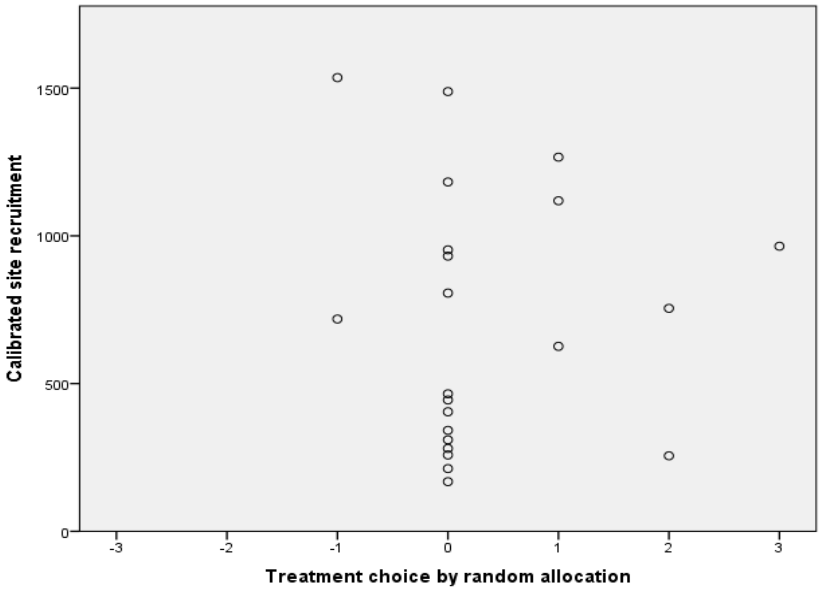


Fig. XXXI: Relationship between additional trial investigations and calibrated site recruitment

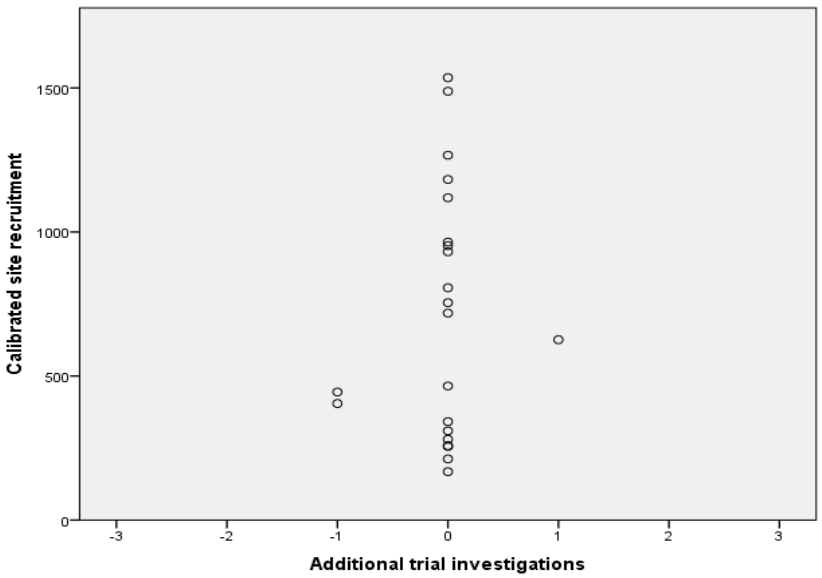


Fig. XXXII: Relationship between additional travel and extra costs and calibrated site recruitment

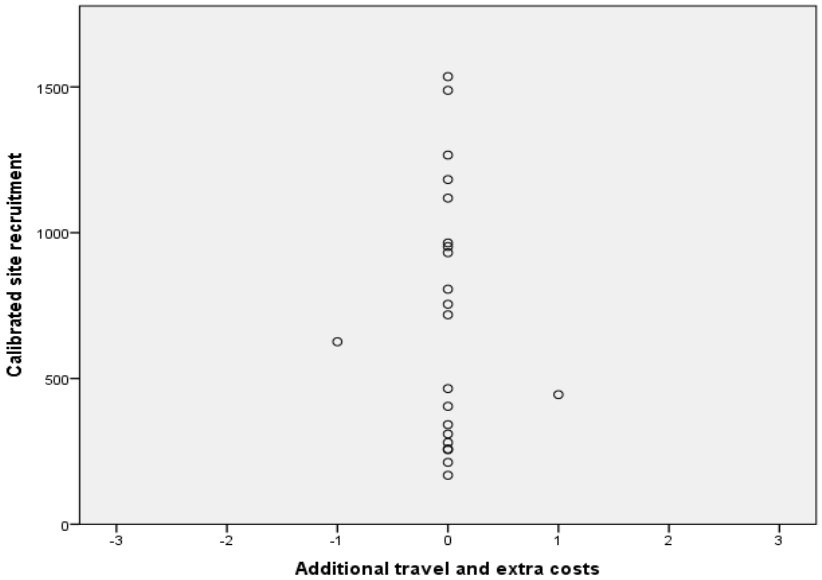


Fig. XXXIII: Relationship between intervention available only in the trial and calibrated site recruitment

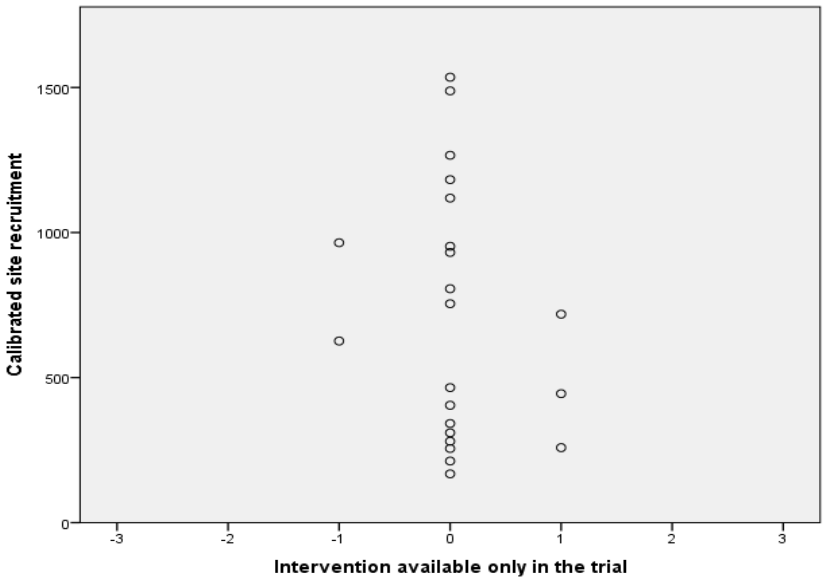


Fig. XXXIV: Relationship between communication between research team and parents and calibrated site recruitment

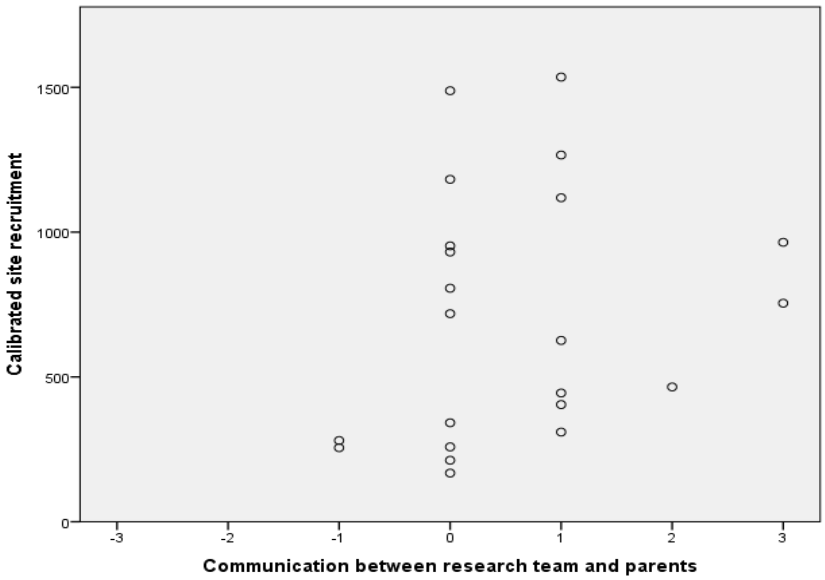
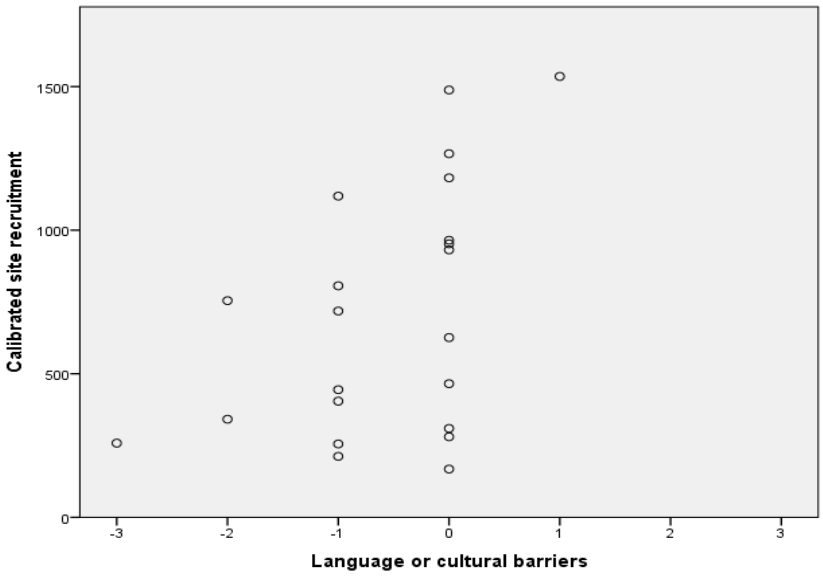


Fig. XXXV: Relationship between language and cultural barriers and calibrated site recruitment



Clinical team related factors

Fig. XXXVI: Relationship between language and cultural barriers and calibrated site recruitment

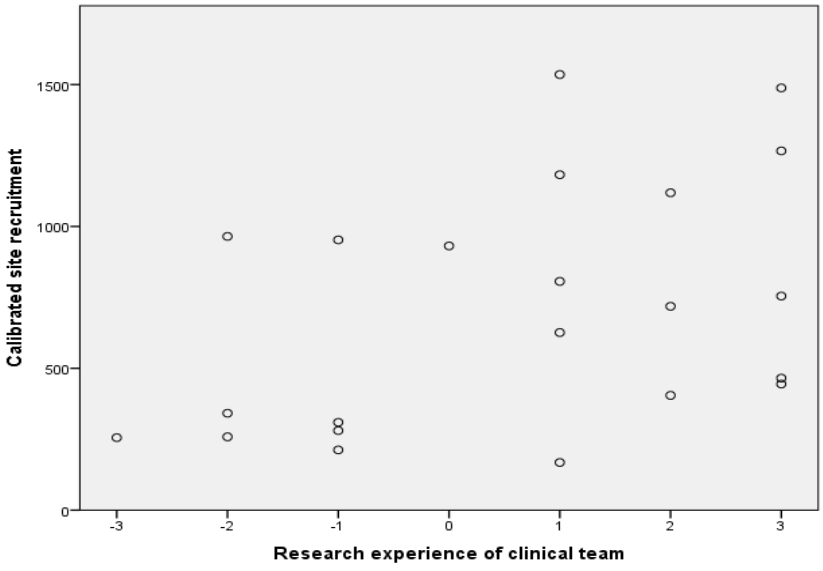


Fig. XXXVII: Relationship between presence of designated research nurse/practitioner and calibrated site recruitment

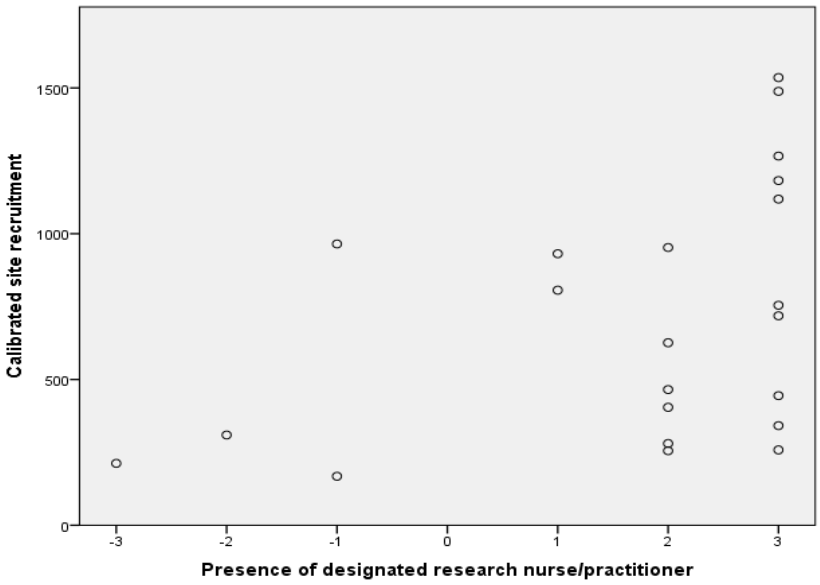


Fig. XXXVIII: Relationship between language and cultural barriers and calibrated site recruitment

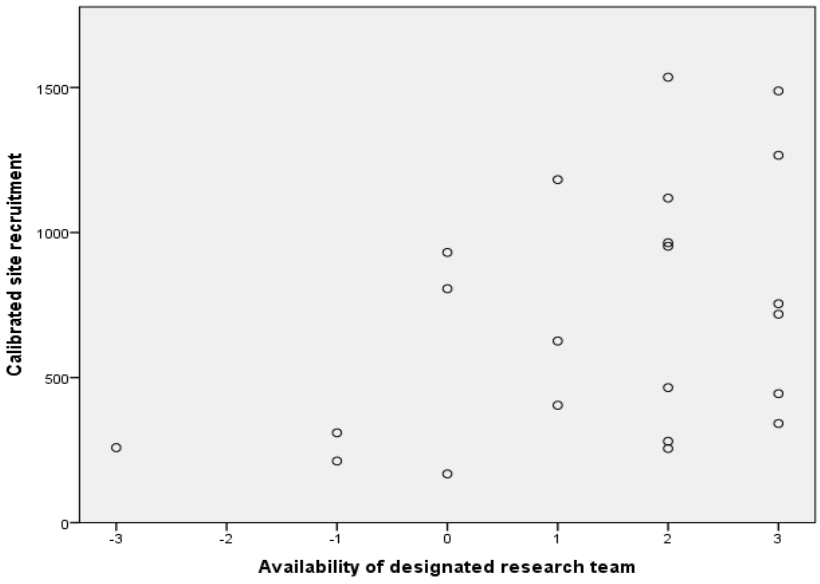


Fig. XXXIX: Relationship between availability of research staff out of hours and calibrated site recruitment

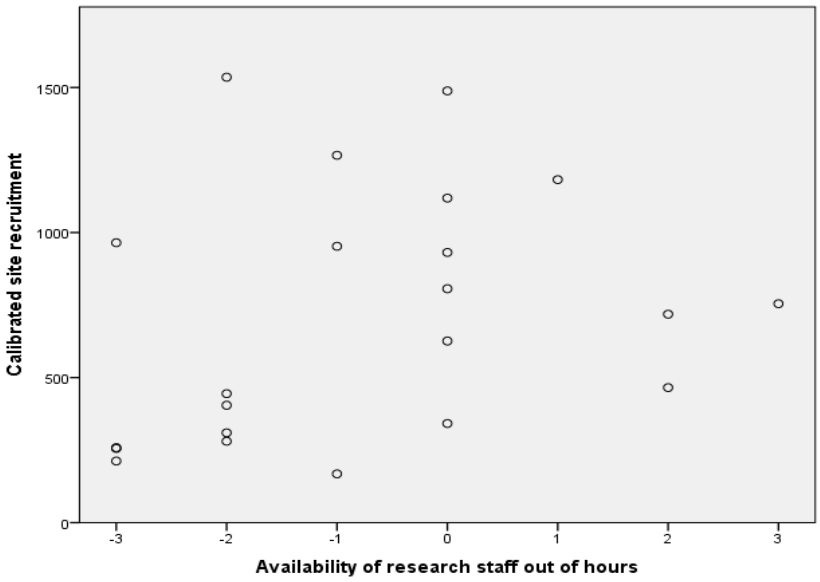


Fig. XL: Relationship between shift patterns of work and calibrated site recruitment

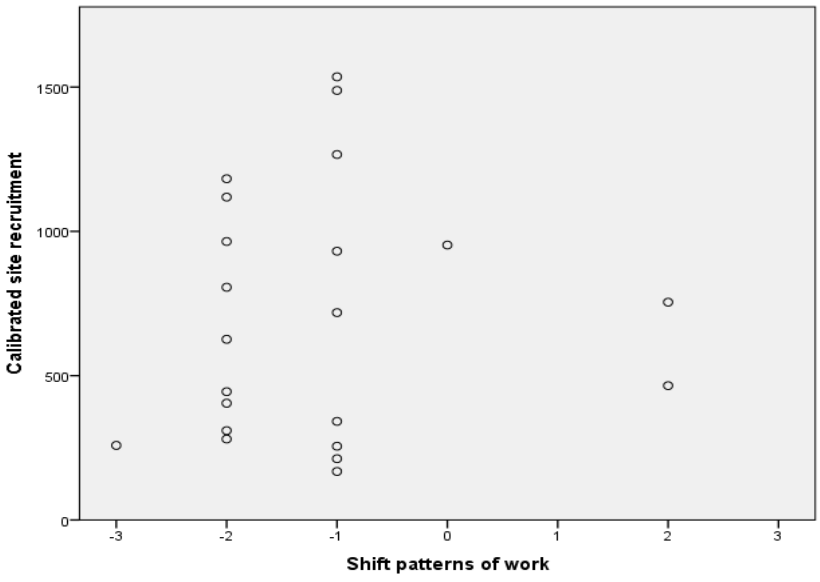


Fig. XLI: Relationship between motivation of clinical team and calibrated site recruitment

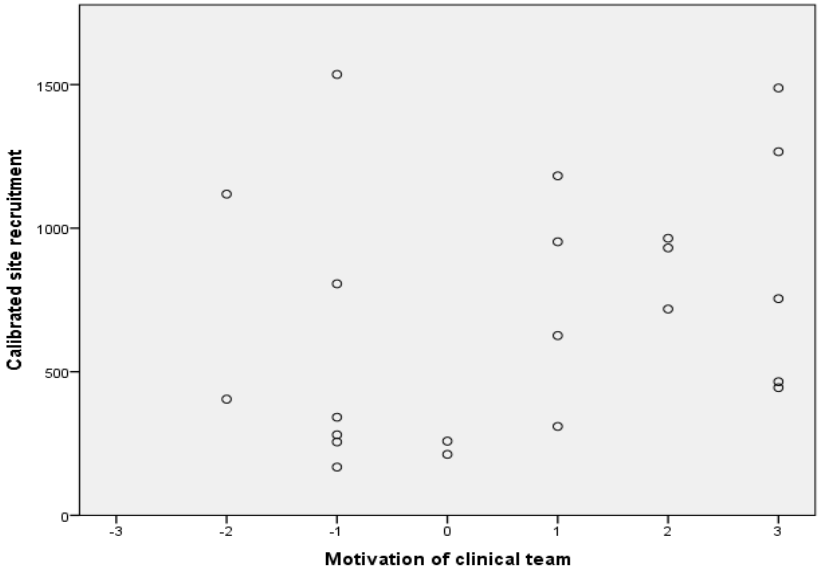


Fig. XLII: Relationship between clinical workload and calibrated site recruitment

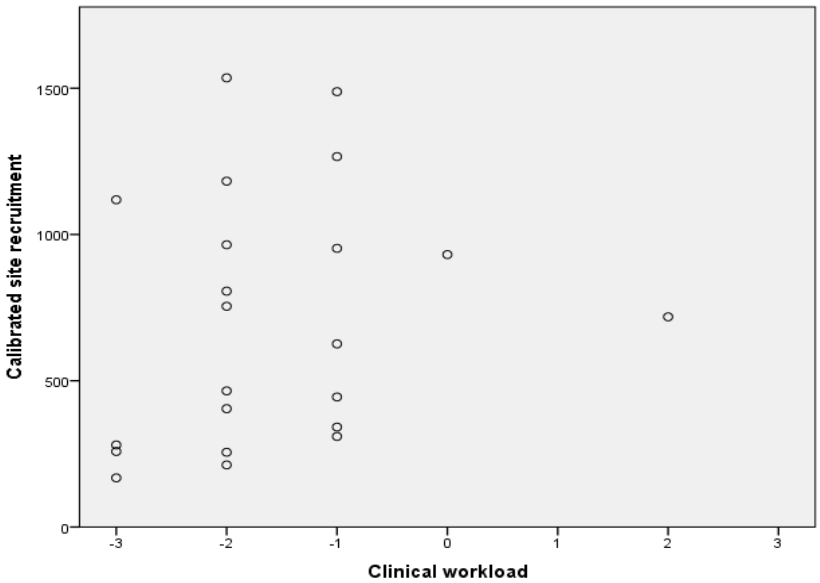


Fig. XLIII: Relationship between language and cultural barriers and calibrated site recruitment

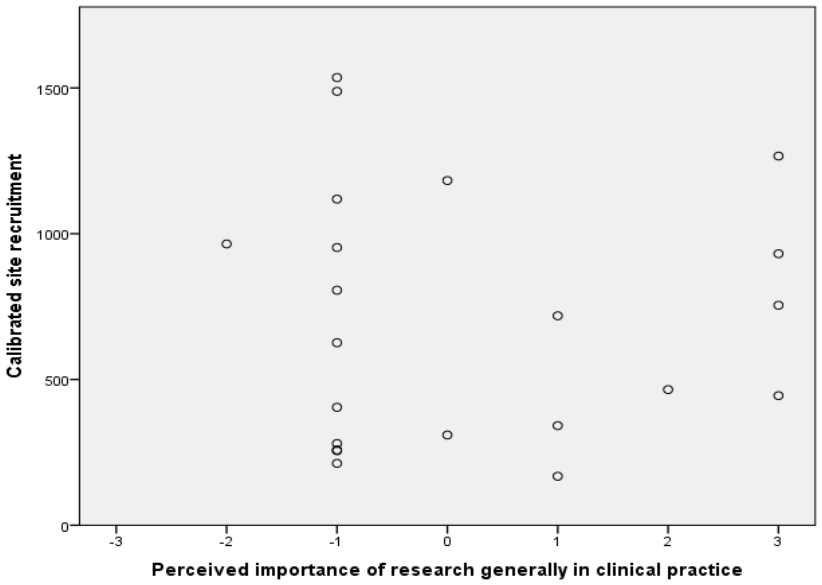


Fig. XLIV: Relationship between perceived importance of research question and calibrated site recruitment

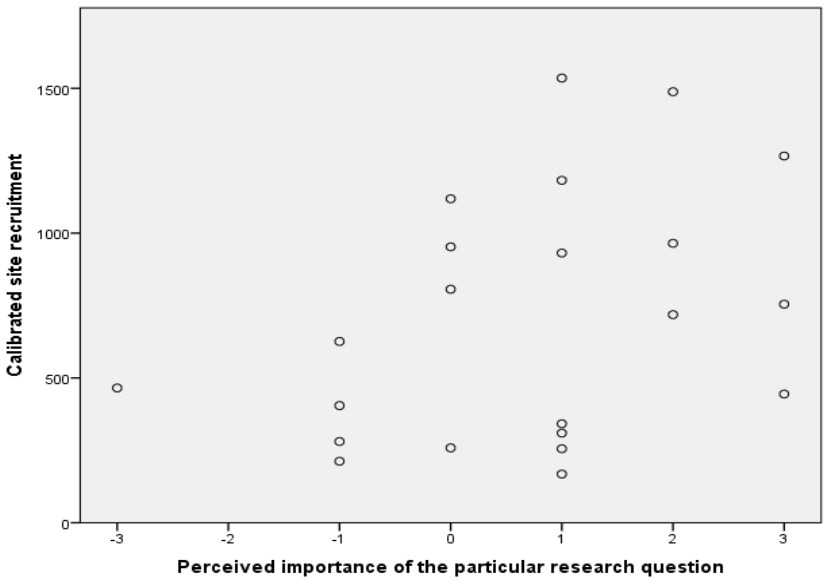


Fig. XLV: Relationship between communication skills of clinical team and calibrated site recruitment

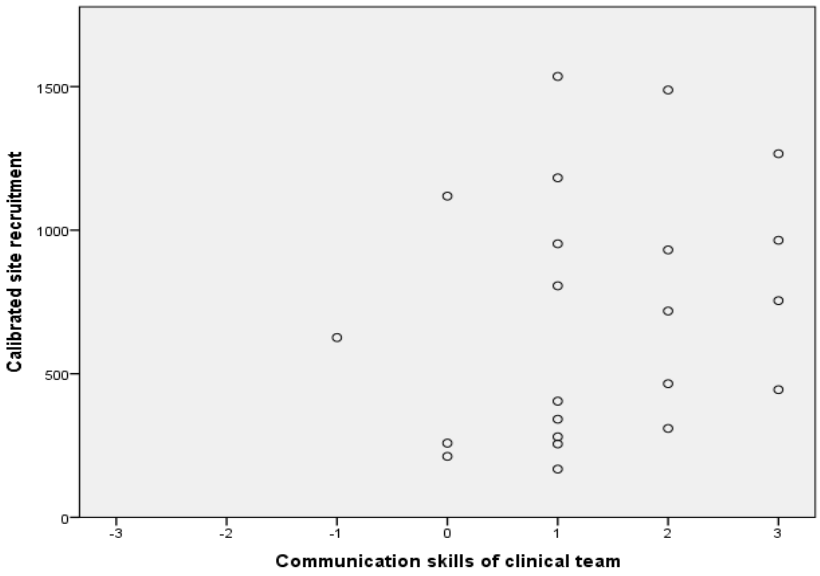


Fig. XLVI: Relationship between clinician preference for particular treatment and calibrated site recruitment

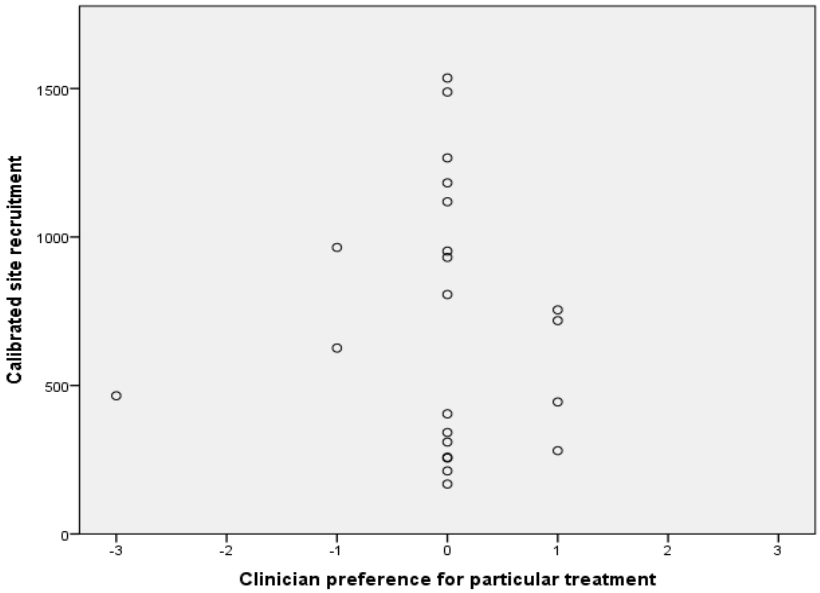


Fig. XLVII: Relationship between clinician attitude to involving patients in research and calibrated site recruitment

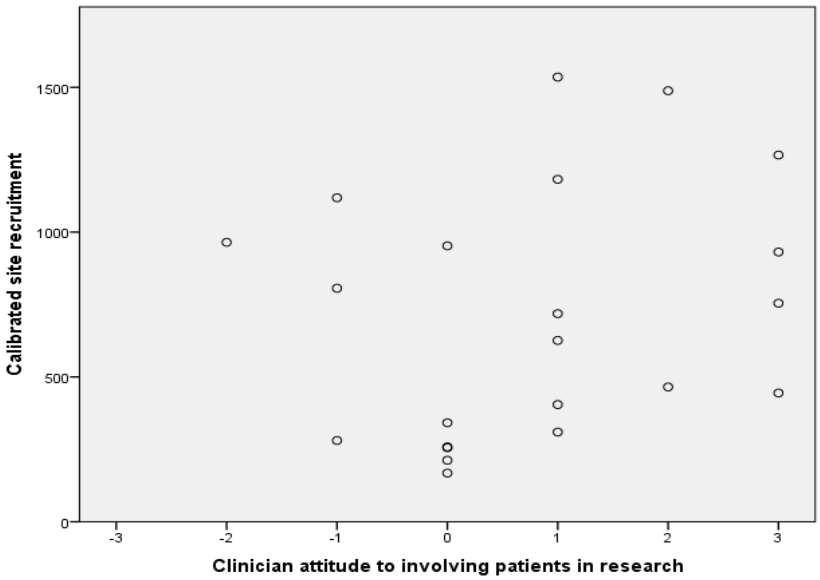


Fig. XLVIII: Relationship between difficulty in approaching patients for consent and calibrated site recruitment

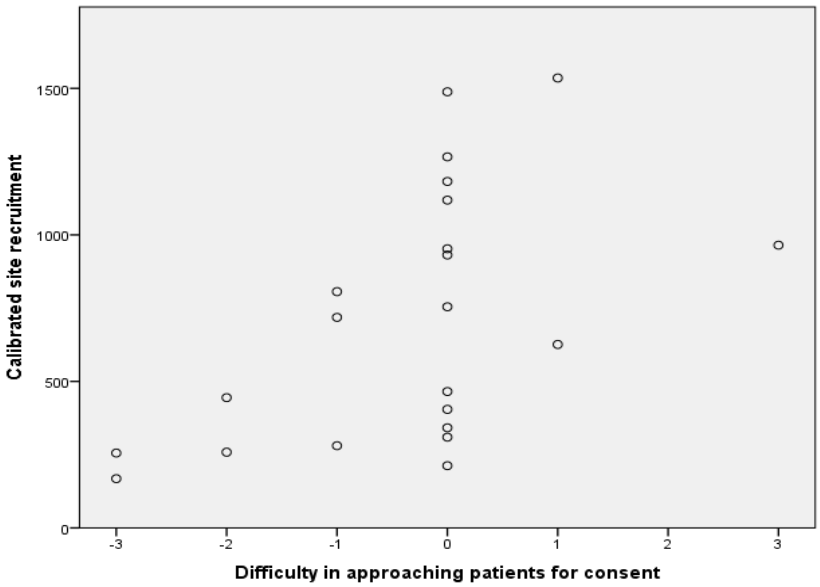


Fig. XLIX: Relationship between amount and complexity of trial information provided and calibrated site recruitment

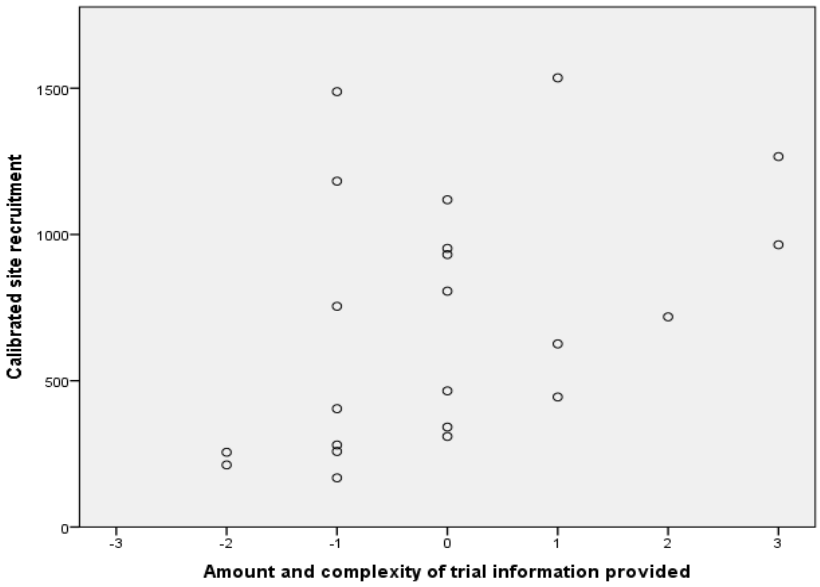


Fig. L: Relationship between clarity in presentation of trial information and calibrated site recruitment

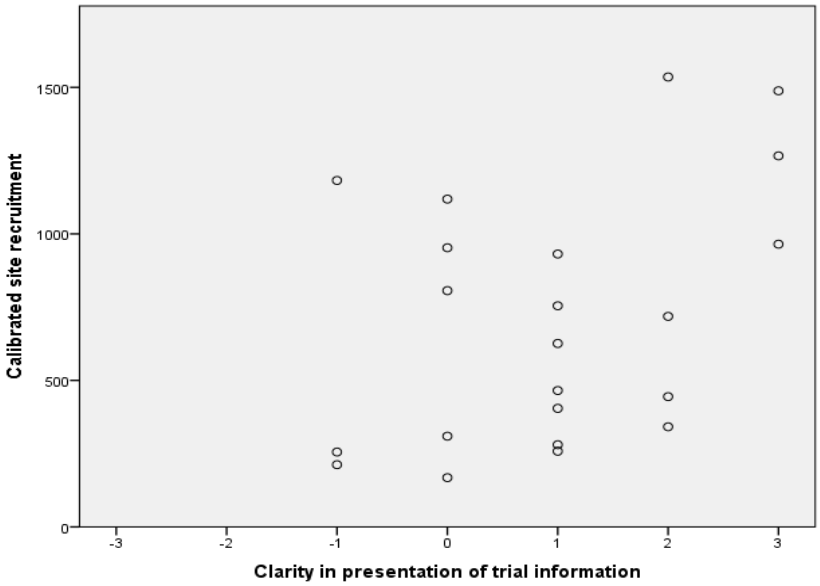


Fig. LI: Relationship between social and emotional dynamics of trial discussion and calibrated site recruitment

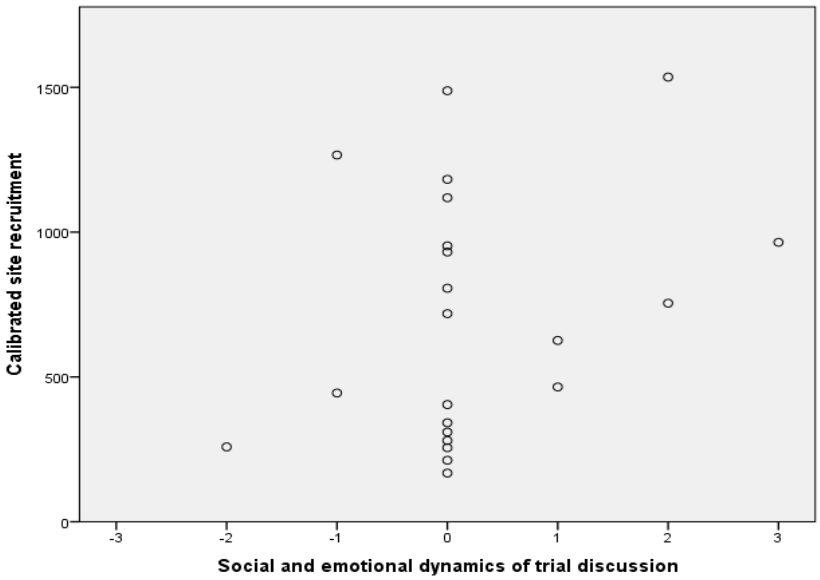


Fig. LII: Relationship between time and setting of consent seeking and calibrated site recruitment

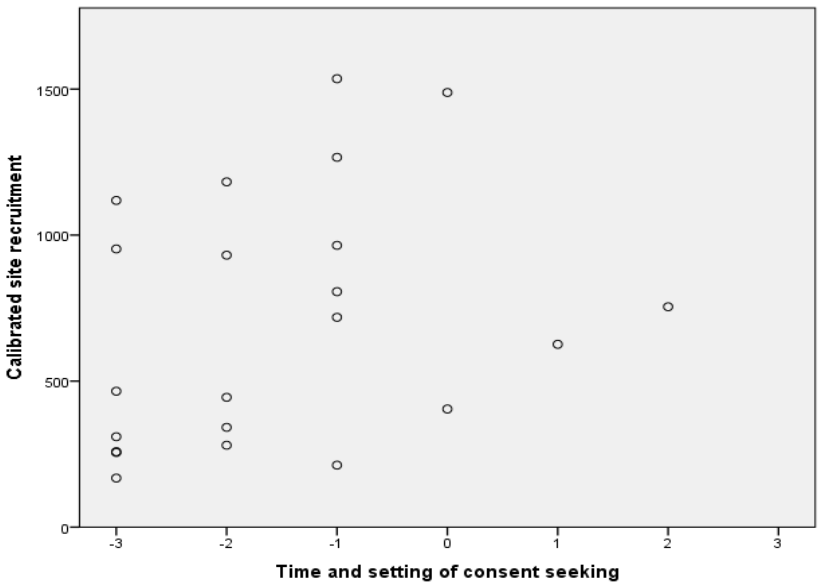


Fig. LIII: Relationship between senior doctors and nurses seeking consent and calibrated site recruitment

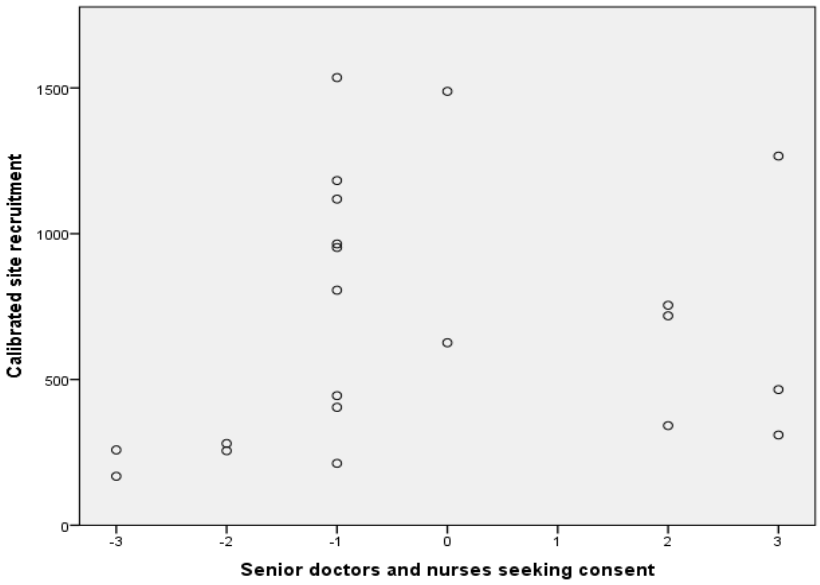
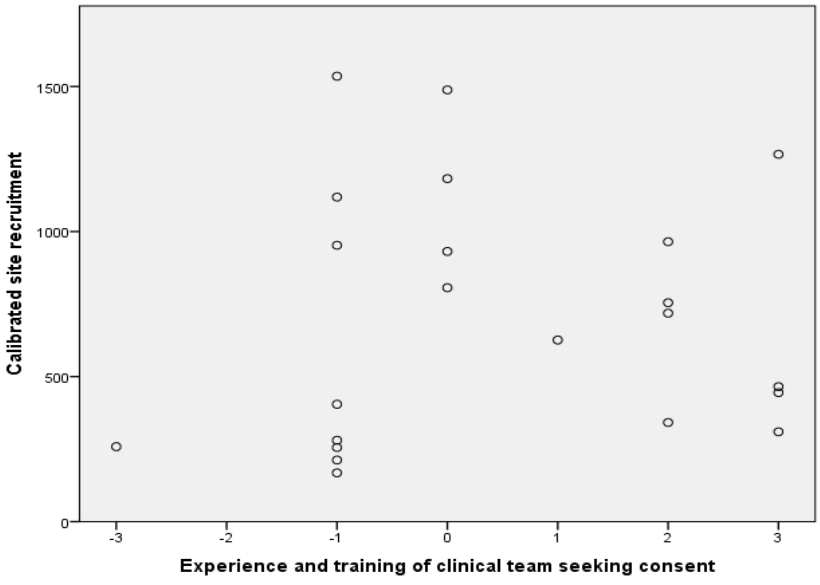


Fig. LIV: Relationship between experience and training of clinical team seeking consent and calibrated site recruitment



Study Team factors

Fig. LV: Relationship between motivation of MAGNETIC team at site and calibrated site recruitment

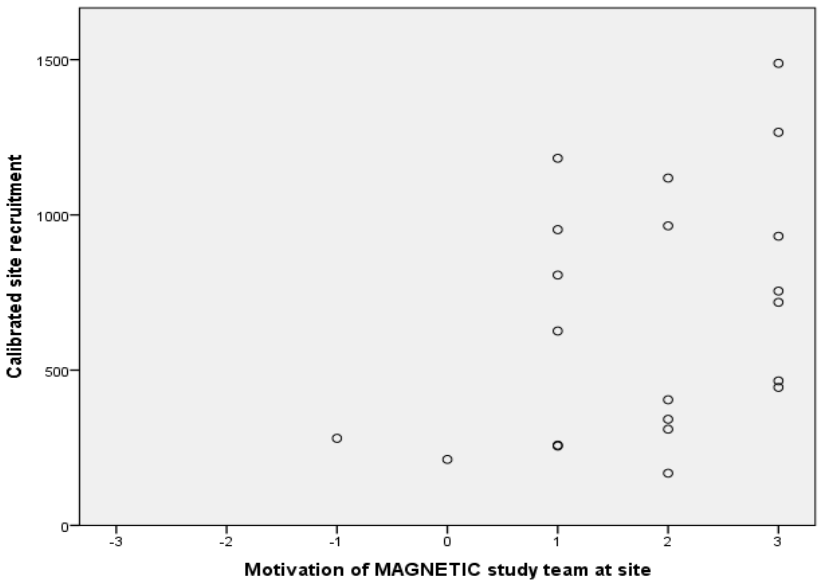


Fig. LVI: Relationship between communication and coordination between study team members at site and calibrated site recruitment

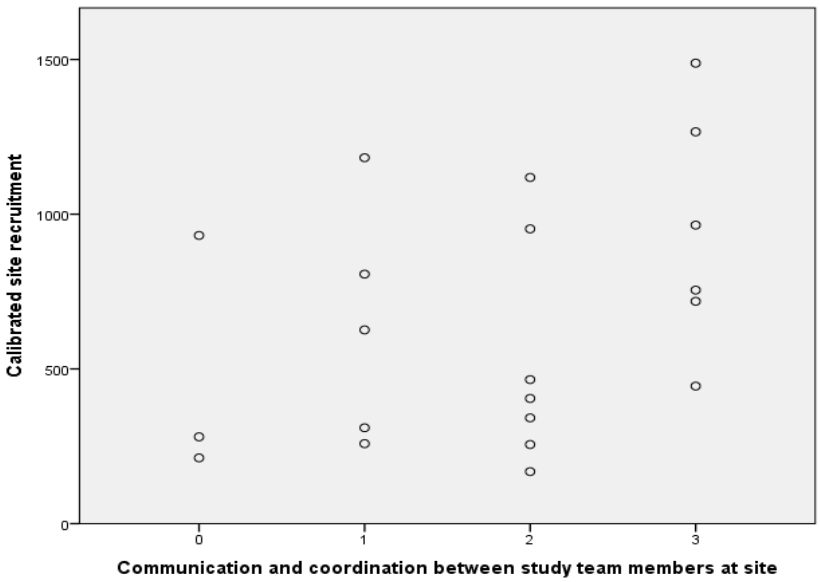


Fig. LVII: Relationship between communication and coordination between study team at site and CTU and calibrated site recruitment

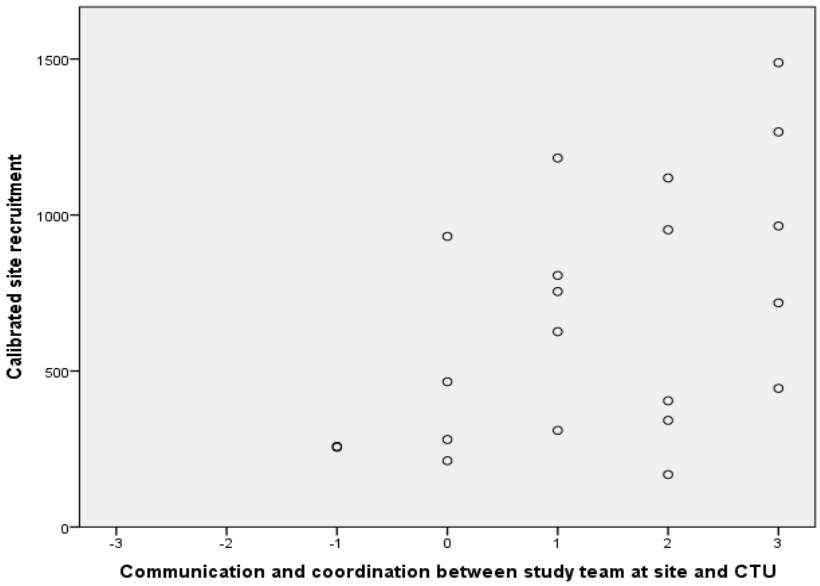
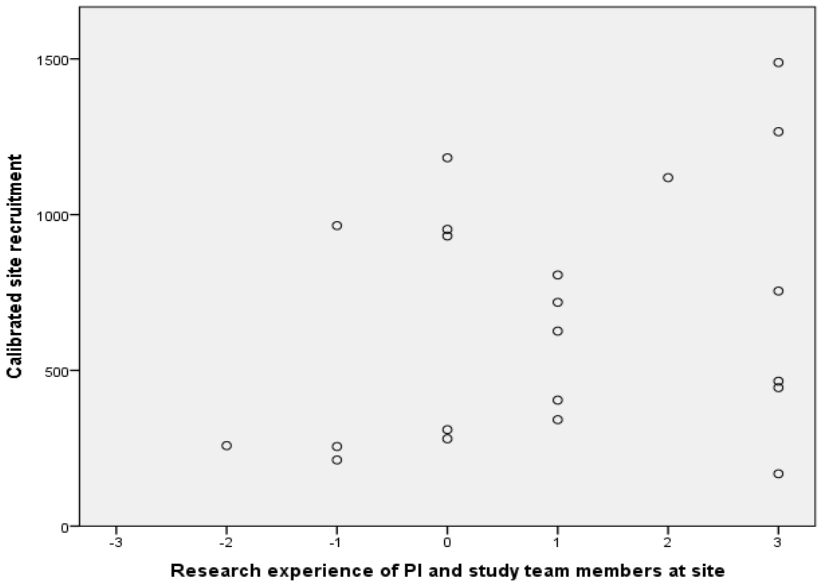
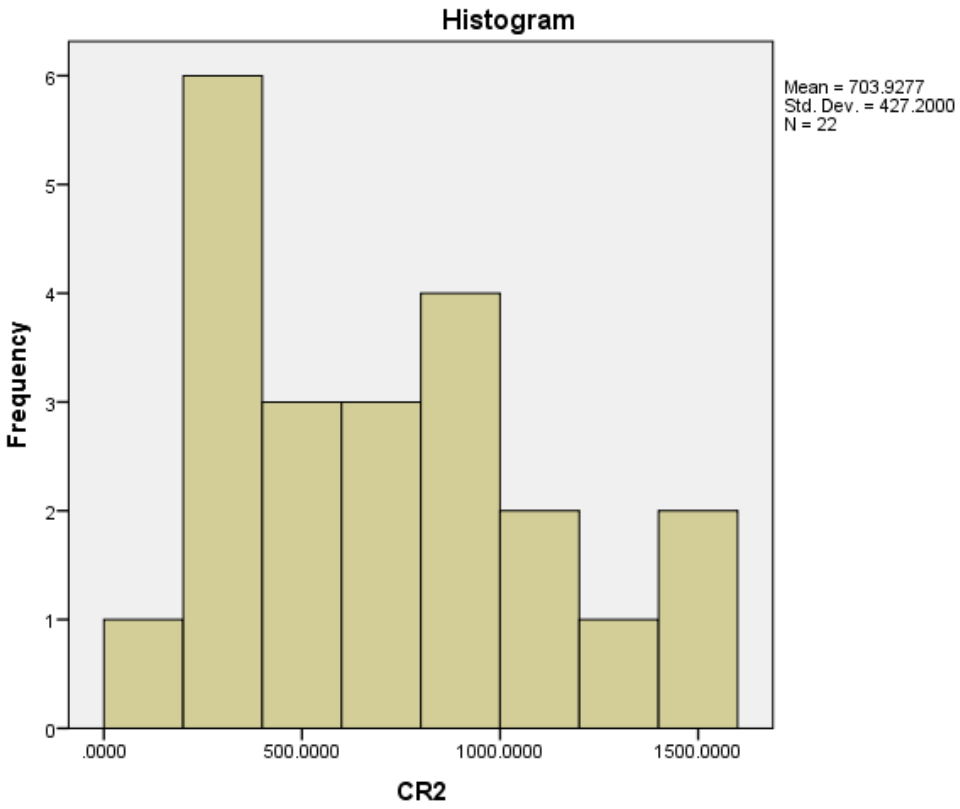


Fig. LVIII: Relationship between research experience of PI and study team at site and calibrated site recruitment



Appendix 23: Histogram showing the distribution of calibrated recruitment at sites



CR2- Calibrated recruitment at sites

Appendix 24: Correlation of calibrated site recruitment with PI responses

Spearman's rank correlation

	Correlation co-efficient	p-value
Trial level factors		
Funding	.336	0.126
Trial design	.462	*0.031*
Patient Inclusion Criteria	.212	0.356
MAGNETIC being a drug trial	.488	*0.021*
Study protocol compared to clinical practice	.184	0.413
Clinical equipoise	.335	0.138
Previous feasibility assessment	.270	0.224
Previous pilot trial	.039	0.867
Publicity by the trial team	.132	0.559
External publicity	.225	0.313
Trial management	.460	*0.031*
Protocol amendments	.098	0.666
Seasonal variation	.238	0.286
Site level factors		
Time to open up site	.035	0.877
Recruitment target	.131	0.561
Time to complete administrative work related to the trial	-.073	0.746
Number of trained staff	.155	0.490
Local clinical arrangements	.402	0.071
Choice of recruitment setting	.504	*0.017*
GCP training	.198	0.378
Data collection process	-.254	0.255
Competing local research projects	-.473	*0.026*
Local research culture	.007	0.974
Patient related factors		
Consent rate	.553	*0.008*
Familiarity with experimental treatment	.262	0.239
Parent's attitude towards their child taking experimental medicine or placebo	.639	*0.001*
Parent's preference for a particular treatment	.402	0.064
Parent's concerns about side effects of new drug	.308	0.163
Duration of trial and follow up	.031	0.891
Treatment choice by random allocation	.035	0.876
Additional trial investigations	.110	0.627
Additional travel and extra costs	-.048	0.834
Intervention available only in the trial	-.220	0.326
Communication between research team and parents	.343	0.118
Clinician influence	.282	0.204
Language or cultural barriers	.426	*0.048*

Clinical team related factors		
Research experience of clinical team	.428	*0.047*
Presence of designated research nurse/practitioner	.442	*0.040*
Availability of designated research team	.407	0.060
Availability of research staff out of hours	.396	0.068
Shift patterns of work	.117	0.605
Motivation of clinical team	.330	0.133
Clinical workload	.288	0.193
Perceived importance of research generally in clinical practice	-.022	0.921
Perceived importance of the particular research question	.362	0.098
Communication skills of clinical team	.310	0.161
Clinician preference for particular treatment	-.129	0.567
Clinician attitude to involving patients in research	.266	0.231
Difficulty in approaching patients for consent	.582	0.004
Information and consent related factors		
Amount and complexity of trial information provided	.507	0.016
Clarity in presentation of trial information	.410	0.058
Social and emotional dynamics of trial discussion	.250	0.262
Time and setting of consent seeking	.354	0.106
Senior doctors and nurses seeking consent	.364	0.105
Experience and training of clinical team seeking consent	.217	0.333
Study team factors		
Motivation of MAGNETIC study team at site	.396	0.076
Communication and coordination between study team members at site	.385	0.085
Communication and coordination between study team at site and CTU	.507	*0.019*
Research experience of PI and study team members at site	.292	0.199

Linear Regression

	R	R-squared	p-value
Trial level factors			
Funding	0.328	0.108	0.136
Trial design	0.416	0.173	0.054
Patient Inclusion Criteria	0.209	0.044	0.363
MAGNETIC being a drug trial	0.447	0.200	*0.037*
Study protocol compared to clinical practice	0.114	0.013	0.612
Clinical equipoise	0.196	0.038	0.395
Previous feasibility assessment	0.281	0.079	0.205
Previous pilot trial	0.071	0.005	0.761
Publicity by the trial team	0.186	0.035	0.407
External publicity	0.275	0.076	0.215
Trial management	0.421	0.177	0.051
Protocol amendments	0.067	0.005	0.766
Seasonal variation	0.285	0.081	0.199
Site level factors			
Time to open up site	0.040	0.002	0.861
Recruitment target	0.096	0.009	0.670
Time to complete administrative work related to the trial	0.035	0.001	0.876
Number of trained staff	0.034	0.001	0.879
Local clinical arrangements	0.335	0.112	0.138
Choice of recruitment setting	0.474	0.225	*0.026*
GCP training	0.178	0.032	0.427
Data collection process	0.206	0.042	0.358
Competing local research projects	0.437	0.191	*0.042*
Local research culture	0.017	0.000	0.940
Patient related factors			
Consent rate	0.534	0.286	*0.010*
Familiarity with experimental treatment	0.274	0.075	0.218
Parent's attitude towards their child taking experimental medicine or placebo	0.639	0.409	*0.001*
Parent's preference for a particular treatment	0.377	0.142	0.084
Parent's concerns about side effects of new drug	0.382	0.146	0.079
Duration of trial and follow up	0.062	0.004	0.784
Treatment choice by random allocation	0.005	0.000	0.983
Additional trial investigations	0.143	0.020	0.526
Additional travel and extra costs	0.066	0.004	0.772
Intervention available only in the trial	0.200	0.040	0.371
Communication between research team and parents	0.223	0.050	0.319
Clinician influence	0.236	0.056	0.291
Language or cultural barriers	0.461	0.213	*0.031*
Clinical team related factors			
Research experience of clinical team	0.416	0.173	0.054
Presence of designated research nurse/practitioner	0.406	0.165	0.06
Availability of designated research team	0.412	0.170	0.057

Availability of research staff out of hours	0.279	0.078	0.208
Shift patterns of work	0.071	0.005	0.754
Motivation of clinical team	0.290	0.084	0.191
Clinical workload	0.196	0.038	0.382
Perceived importance of research generally in clinical practice	0.023	0.001	0.921
Perceived importance of the particular research question	0.365	0.133	0.095
Communication skills of clinical team	0.235	0.055	0.293
Clinician preference for particular treatment	0.011	0.000	0.960
Clinician attitude to involving patients in research	0.214	0.046	0.339
Difficulty in approaching patients for consent	0.520	0.271	*0.013*
Information and consent related factors			
Amount and complexity of trial information provided	0.425	0.181	*0.049*
Clarity in presentation of trial information	0.403	0.162	0.063
Social and emotional dynamics of trial discussion	0.295	0.087	0.183
Time and setting of consent seeking	0.287	0.082	0.195
Senior doctors and nurses seeking consent	0.153	0.024	0.507
Experience and training of clinical team seeking consent	0.057	0.003	0.801
Study team factors			
Motivation of MAGNETIC study team at site	0.381	0.146	0.088
Communication and coordination between study team members at site	0.356	0.126	0.114
Communication and coordination between study team at site and CTU	0.499	0.249	*0.021*
Research experience of PI and study team members at site	0.291	0.085	0.201

Appendix 25: Papers citing the recruitment survey tool described in Chapter 4

1. Kaur, G., Hutchison, I., Mehanna, H., Williamson, P., Shaw, R., & Smith, C. T. (2013). Barriers to recruitment for surgical trials in head and neck oncology: a survey of trial investigators. *BMJ open*, *3*(4), e002625.
2. Techau, M., Lunde, A., Pedersen, C. G., Green, A., Johannessen, H., & Nissen, N. (2014). Non-participants and reasons for non-participation in a pragmatic trial of energy healing as cancer rehabilitation. *European Journal of Integrative Medicine*, *6*(3), 268-276.
3. Gamble, C., Dudley, L., Allam, A., Bell, P., Goodare, H., Hanley, B., ... & Young, B. (2014). Patient and public involvement in the early stages of clinical trial development: a systematic cohort investigation. *BMJ open*, *4*(7), e005234.
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5. Smith, T., Maidment, I., Hebding, J., Madzima, T., Cheater, F., Cross, J., ... & Fox, C. (2014). Systematic review investigating the reporting of comorbidities and medication in randomized controlled trials of people with dementia. *Age and ageing*, *43*(6), 868-872.
6. Mann, C., Delgado, D., & Horwood, J. (2014). Evaluation of internal peer-review to train nurses recruiting to a randomized controlled trial–Internal Peer-review for Recruitment Training in Trials (InterPReTiT). *Journal of advanced nursing*, *70*(4), 777-790.
7. Cheema, B. S., Davies, T. B., Stewart, M., Papalia, S., & Atlantis, E. (2015). The feasibility and effectiveness of high-intensity boxing training versus moderate-intensity brisk walking in adults with abdominal obesity: a pilot study. *BMC sports science, medicine and rehabilitation*, *7*(1), 3.
8. Gheorghe, A. (2014). *The influence of centre selection on the generalisability of economic evaluations conducted alongside randomised controlled trials: a case study from the Rossini trial* (Doctoral dissertation, University of Birmingham).
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10. Smyth, R. M., Jacoby, A., Altman, D. G., Gamble, C., & Williamson, P. R. (2015). The natural history of conducting and reporting clinical trials: interviews with trialists. *Trials*, *16*(1), 16.
11. Hubbard, G., Campbell, A., Davies, Z., Munro, J., Ireland, A. V., Leslie, S., ... & Treweek, S. (2015). Experiences of recruiting to a pilot trial of Cardiac Rehabilitation In patients with Bowel cancer (CRIB) with an embedded process evaluation: lessons learned to improve recruitment. *Pilot and Feasibility Studies*, *1*(1), 1-12.

12. Keightley, A., Clarkson, J., Maguire, A., Speed, C., & Innes, N. (2014). Participant recruitment to FiCTION, a primary dental care trial–survey of facilitators and barriers. *British dental journal*, *217*(10), E22-E22.
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Appendix 26: Requests for permission to use the recruitment survey tool described in Chapter 4

03/05/2015

I would like to start my email by introducing myself. I am Rula Museli, a MSc student-Clinical Research at the University of Liverpool. And I am at the final stage- the dissertation- to graduate. I choose "Clinical Trials in Jordan: A Survey on Cancer Adult Patients to Determine Factors Affecting Patients' Recruitment into Clinical Trials" as a topic for my dissertation.
Now, I am trying to prepare the survey and I found the one your honor and your colleagues had already developed and was published in a paper under a title: "Developing a survey of barriers and facilitators to recruitment in randomized controlled trials" in Trials, 2012, 13: 218.
I am interested in the "Recruitment Survey" and would like to ask if your kindness allow me to use part of it for the survey for my MSc degree.
I appreciate your consideration.
Best Regards,
Rula Museli

05/03/2015

Dear Ms. Kaur
I am writing to seek your permission in using the survey you designed and published. I am doing my Masters dissertation in clinical research, and I work in paediatric palliative care at Great Ormond Street Hospital. To give you a bit of background, there have been no clinical trials within paediatric palliative care, which is an area that is growing in terms of qualitative research, but very little in seeking to establish an evidence base in clinical practice. I would be most grateful if you permit me to use your questionnaire, which will be used within Great Ormond Street surveying the view of clinicians and senior nurses.

Once again thank you for your time, and I look forward to hearing from you.

Maggie Comac

19/01/2015

Dear Dr Kaur
I have recently read your paper about the web based survey you developed to assess professionals experience in recruiting to trials. I am currently working with colleagues at the University of Leeds in the Leeds Institute of Health Science and the Institute of Clinical Trials on a feasibility study which is reliant on adequate recruitment to the trial. I was wondering if you would be able to share a copy of your survey with us for us to consider how we could use it to assess the experience of teams in future trials. Is it available more widely for sharing yet? I look forward to hearing from you.
Best wishes
Janine

Dr Janine Bestall
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LS2 9LJ
Phone: 0113 343 5114; e-mail:J.bestall@leeds.ac.uk

14/10/2015

Hi Geetinder
I have just read Kaur et al.: Developing a survey of barriers and facilitators to recruitment in randomized controlled trials. Trials 2012 13:218. I wondered if your questionnaire would be helpful for our study and so wish to know if it is publicly available? We currently have 3 sites involved in our pilot study and plan to conduct a larger effectiveness trial. It is funded by NIHR HS-DR.
Best Wishes
Gill

Dr Gill Hubbard
Reader & Co-Director
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20/01/14

Hello Dr. Kaur,
I read your "Developing a survey pf barriers..." paper and I am wondering if you have a paper in progress or completed on the results of your survey that you would be willing to share? We are considering using your survey and would like to know the results of your study. Thank you, Janice Sabin
Janice A. Sabin, PhD, MSW
Research Assistant Professor, University of Washington Department of Biomedical Informatics and Medical Education Box 357240 Seattle, WA 98195 206-616-9421, (c) 206-851-7938 http://faculty.washington.edu/sabinja/index.html

08/08/2013

I just read your article in trialsjournal and am very interested. Is it possible for you to send me the actual survey? I am a patient advocate who is involved with the development of clinical trials, and I think this might be of interest to our research group.

Thank you for considering my request.

Nancy

Nancy Roach
www.FightColorectalCancer.org

Appendix 27: Copy of publications arising from work in this thesis