

## **Recruitment to randomised trials: strategies for trial enrolment and participation study. The STEPS study**

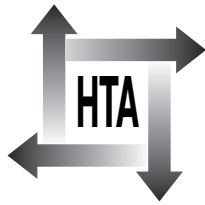
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# Recruitment to randomised trials: strategies for trial enrolment and participation study. The STEPS study

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The research reported in this monograph was commissioned by the National Coordinating Centre for Research Methodology (NCCRM), and was formerly transferred to the HTA Programme in April 2007 under the newly established NIHR Methodology Panel. The HTA Programme project number is 06/90/13. The contractual start date was in March 2003. The draft report began editorial review in March 2007 and was accepted for publication in April 2007. The commissioning brief was devised by the NCCRM who specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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## Abstract

### Recruitment to randomised trials: strategies for trial enrolment and participation study. The STEPS study

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**Objectives:** To identify factors associated with good and poor recruitment to multicentre trials.

**Data sources:** Part A: database of trials started in or after 1994 and were due to end before 2003 held by the Medical Research Council and Health Technology Assessment Programmes. Part B: interviews with people playing a wide range of roles within four trials that their funders identified as 'exemplars'. Part C: a large multicentre trial (the CRASH trial) of treatment for head injury.

**Review methods:** The study used a number of different perspectives ('multiple lenses'), and three components. Part A: an epidemiological review of a cohort of trials. Part B: case studies of trials that appeared to have particularly interesting lessons for recruitment. Part C: a single, in-depth case study to examine the feasibility of applying a business-orientated analytical framework as a reference model in future trials.

**Results:** In the 114 trials found in Part A, less than one-third recruited their original target within the time originally specified, and around one-third had extensions. Factors observed more often in trials that recruited successfully were: having a dedicated trial manager, being a cancer or drug trial, and having interventions only available inside the trial. The most commonly reported strategies to improve recruitment were newsletters and mailshots, but it was not possible to assess whether they were causally linked to changes in recruitment. The analyses in Part B suggested that successful trials were those addressing clinically important questions at a timely point. The investigators were held in high esteem by the interviewees, and the trials were firmly grounded in existing clinical practices, so that the trial processes were not alien to clinical collaborators, and the results

could be easily applicable to future practice. The interviewees considered that the needs of patients were well served by participation in the trials. Clinical collaborators particularly appreciated clear delineation of roles, which released them from much of the workload associated with trial participation. There was a strong feeling from interviewees that they were proud to be part of a successful team. This pride fed into further success. Good groundwork and excellent communications across many levels of complex trial structures were considered to be extremely important, including training components for learning about trial interventions and processes, and team building. All four trials had faced recruitment problems, and extra insights into the working of trials were afforded by strategies invoked to address them. The process of the case study in Part C was able to draw attention to a body of research and practice in a different discipline (academic business studies). It generated a reference model derived from a combination of business theory and work within CRASH. This enabled identification of weaker managerial components within CRASH, and initiatives to strengthen them. Although it is not clear, even within CRASH, whether the initiatives that follow from developing and applying the model will be effective in increasing recruitment or other aspects of the success of the trial, the reference model could provide a template, with potential for those managing other trials to use or adapt it, especially at foundation stages. The model derived from this project could also be used as a diagnostic tool if trials have difficulties and hence as a basis for deciding what type of remedial action to take. It may also be useful for auditing the progress of trials, such as during external review.

**Conclusions:** While not producing sufficiently definitive results to make strong recommendations, the work here suggests that future trials should consider the different needs at different phases in the life of trials, and place greater emphasis on 'conduct' (the process of actually doing trials). This implies learning lessons from successful trialists and trial managers, with better training for issues relating to trial conduct. The complexity of large trials means that unanticipated difficulties are highly likely at some time in every trial. Part B suggested that successful trials were those flexible and robust enough to adapt to unexpected

issues. Arguably, the trialists should also expect agility from funders within a proactive approach to monitoring ongoing trials. Further research into different recruitment patterns (including 'failures') may help to clarify whether the patterns seen in the 'exemplar' trials differ or are similar. The reference model from Part C needs to be further considered in other similar and different trials to assess its robustness. These and other strategies aimed at increasing recruitment and making trials more successful need to be formally evaluated for their effectiveness in a range of trials.



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## List of abbreviations

|         |  |        |   |
|---------|--|--------|---|
| A&E     | accident and emergency   | MBA    | Master of Business Administration                           |
| BHF     | British Heart Foundation   | MRC    | Medical Research Council                                    |
| CAMHS   | Child and Adolescent Mental Health Services  | MREC   | multicentre research ethics committee                       |
| CI      | confidence interval  | NA     | not applicable  |
| CRASH   | Corticosteroid Randomisation After Significant Head Injury   | NCCHTA | National Coordinating Centre for the HTA Programme          |
| CTSU    | Clinical Trial Service Unit  | NCCRM  | National Coordinating Centre for Research Methodology       |
| DMC     | data monitoring committee  | NCRN   | National Cancer Research Network                            |
| DMEC    | data monitoring and ethics committee   | NICE   | National Institute for Health and Clinical Excellence       |
| ELEVATE | A pragmatic single-blind RCT and health economic evaluation of leukotriene receptor antagonists in primary care at steps two and three of the National Asthma Guidelines | OR     | odds ratio  |
| FOCUS   | Trial of Chemotherapy for Bowel Cancer [Fluorouracil, Oxaliplatin and Irinotecan (CPT11), Use and Sequencing]  | ORACLE | Role of Antibiotics in Curtailing Labour and Early Delivery |
| 5-FU    | 5-fluorouracil   | PCT    | primary care trust  |
| GI      | gastrointestinal   | PI     | principal investigator                                      |
| HPS     | Heart Protection Study   | R&D    | research and development                                    |
| ICS     | inhaled corticosteroid   | RCT    | randomised controlled trial                                 |
| LAB     | long-acting beta-agonist   | REC    | research ethics committee                                   |
| LREC    | local research ethics committee  | STEPS  | Strategies for Trials Enrolment and Participation Study     |
| LTRA    | leukotriene receptor antagonist  | TOuCAN | Trial of Outcome for Child and Adolescent Anorexia Nervosa  |
|         |  | TSC    | trial steering committee                                    |

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.





## Executive summary

### Background

Randomised controlled trials are widely accepted as the gold standard for evaluating healthcare interventions. If, however, the target sample size is not achieved, the trial's results will usually be less reliable. If recruitment has to be extended to reach the required sample size, this will delay the use of the results in clinical practice, and usually cost more, so fewer trials can be conducted within the limited resources available.

### Objectives

It is unclear why certain trials recruit well whereas others do not. The aim was, therefore, to identify factors associated with good and poor recruitment to multicentre trials.

### Methods

The study used a number of different perspectives ('multiple lenses'), and three components: Part A: an epidemiological review of a cohort of trials funded by the UK's Medical Research Council (MRC) and Health Technology Assessment (HTA) Programme; Part B: case studies of trials that appeared to have particularly interesting lessons for recruitment; and Part C: a single, in-depth case study of a large multicentre trial to examine the feasibility of applying a business-orientated analytical framework as a reference model in future trials.

Part A was based on 114 multicentre MRC and HTA Programme trials that started in or after 1994 and were due to end before 2003.

Whereas in Part A the planned level of recruitment was used as a surrogate measure for the 'success' of a trial, Part B was based on in-depth analyses of 45 interviews with people playing a wide range of roles within four trials that their funders identified as 'exemplars' (trials which had met, or were scheduled to meet, agreed targets and that the funders publicised as successes).

Part C complements the emphasis on trial 'processes' in Parts A and B in a case study of a large multicentre trial (the CRASH trial) of treatment for head injury.

### Results

In the trials found in Part A, less than one-third recruited their original target within the time originally specified, and around one-third had extensions. Factors observed more often in trials that recruited successfully were: having a dedicated trial manager; being a cancer or drug trial, and having interventions only available inside the trial. However, these findings should be interpreted cautiously: the confidence intervals were wide; associations were, at best, only marginally statistically significant; and the trend for some factors was towards a negative association. The most commonly reported strategies to improve recruitment were newsletters and mailshots, but it was not possible to assess whether they were causally linked to changes in recruitment.

The analyses in Part B suggested that successful trials were those addressing clinically important questions at a timely point. The investigators were held in high esteem by the interviewees, and the trials were firmly grounded in existing clinical practices, so that the trial processes were not alien to clinical collaborators, and the results could be easily applicable to future practice. The interviewees considered that the needs of patients were well served by participation in the trials. Clinical collaborators particularly appreciated clear delineation of roles, which released them from much of the workload associated with trial participation. There was a strong feeling from interviewees that they were proud to be part of a successful team. This pride fed into further success. Good groundwork and excellent communications across many levels of complex trial structures were considered to be extremely important, including training components for learning about trial interventions and processes, and team building. All four trials had faced recruitment problems, and extra insights into the working of trials were afforded by strategies invoked to address them. Teams within trials that

were not exemplars were not interviewed, and hence it is not known to what extent the perceptions observed in these exemplars differed from those in trials that were less successful.

The process of the case study in Part C was able to draw attention to a body of research and practice in a different discipline (academic business studies). It generated a reference model derived from a combination of business theory and work within CRASH. This enabled identification of weaker managerial components within CRASH, and initiatives to strengthen them. Although it is not clear, even within CRASH, whether the initiatives that follow from developing and applying the model will be effective in increasing recruitment or other aspects of the success of the trial, the reference model could provide a template, with potential for those managing other trials to use or adapt it, especially at foundation stages. The model derived from this project could also be used as a diagnostic tool if trials have difficulties and hence as a basis for deciding what type of remedial action to take. It may also be useful for auditing the progress of trials, such as during external review.

## Conclusions

While not producing sufficiently definitive results to propose strong recommendations, the work here suggests that people undertaking future trials ought at least to think about the different needs at different phases in the life of trials, and

place greater emphasis on ‘conduct’ (the process of actually doing trials). This implies learning lessons from successful trialists and trial managers, with better training for issues relating to trial conduct.

The complexity of large trials means that unanticipated difficulties are highly likely at some time in every trial. Part B suggested that successful trials were those flexible and robust enough to adapt to unexpected issues. Arguably, the trialists should also expect agility from funders within a proactive approach to monitoring ongoing trials.

## Recommendations for research

Three important areas for further research arise. First, an extension of Part B to trials with different recruitment patterns (including ‘failures’) may help to clarify whether the patterns seen in the ‘exemplar’ trials differ or are similar. Second, Part C was based around a single large trial with the unusual feature that patients were mainly unconscious. Before use as an audit tool for diagnosing and/or addressing management factors, the reference model needs to be considered in other similar and different trials to assess its robustness. Finally, these and other strategies aimed at increasing recruitment and making trials more successful need to be formally evaluated for their effectiveness in a range of trials.

# Chapter I

## Introduction

### Background

#### The importance of the randomised controlled trial

The randomised controlled trial (RCT) is widely accepted as the gold-standard design for evaluating healthcare interventions.<sup>1,2</sup> Its principal benefits are widely known; for example, the groups generated should only differ by chance in baseline prognostic variables, the potential for attribution is maximised and the results can be analysed using standard statistical testing. Decision-makers are increasingly looking to the results of RCTs to guide practice, and RCTs are now a major and increasing component of NHS-supported research and non-commercially funded research more generally.<sup>3</sup> For example, the UK Medical Research Council (MRC), in its recent review of clinical trials, considers that RCTs are the “most scientifically rigorous, unbiased way of comparing alternative healthcare interventions”.<sup>4</sup>

#### Successful delivery of RCTs

It is important that trials are conducted ethically and efficiently. However, several issues can hamper the successful delivery of trials. These include barriers to patient participation, barriers to clinician participation, poor design, poor conduct, poor analysis, poor reporting and other obstacles such as complex consent procedures.<sup>5</sup> One of the most commonly reported problems with the conduct of multicentre RCTs, however, is that recruitment is slower or more difficult than expected, with many trials failing to reach their planned sample size within the timescale and funding originally envisaged.<sup>6</sup> If the target sample size is not achieved, the trial has less statistical power to detect potentially important clinical differences between the groups, so the results may be less useful.<sup>7</sup> In addition, if recruitment has to be extended to reach the required sample size, the trial will cost more and take longer, delaying the use of the results in clinical practice. If trials become more expensive and take longer, fewer trials can be conducted overall with the limited funding and resources available, and hence less information will be available to the NHS. There is growing policy concern in the UK that trials are increasingly not achieving planned recruitment targets.

To recruit successfully to an RCT depends on a number of factors beyond that of a good design, including: (1) the formal authorisation of the trial, for example by research ethics committees (RECs); (2) the active participation of clinicians or collaborating researchers; and (3) the participation of patients. There has been considerable discussion about whether patients are increasingly less willing to participate in RCTs.<sup>8,9,10</sup> If, however, steps (1) and (2) are not fulfilled, then patients are unlikely to be in a position either to refuse or to accept participation. For the formal authorisation of a trial, REC and NHS Research and Development (R&D) approval is generally required, which can often be a lengthy process. In addition, successful participation of clinicians generally requires the fulfilment of a number of key roles: that they agree to participate in the RCT when invited, offer participation in the trial to eligible patients, recruit eligible patients, and comply with the procedures outlined in the trial protocol.<sup>5</sup> Each of these stages represents a potential barrier to the successful delivery of a trial.

The reasons why certain trials recruit well while others do not remain unclear. Several potential limiting factors have been identified in the literature,<sup>5</sup> including constraints on clinician time,<sup>11,12</sup> lack of available staff,<sup>13</sup> impact on clinician autonomy and complexity of trial procedures.<sup>14</sup> Most of these factors were identified from surveys of researchers or clinicians involved in research, and are summarised in reviews.<sup>5,15</sup> Qualitative work in selected perinatal trials explored the factors that influenced doctors' willingness to propose the trial to parents.<sup>16</sup> Some of the key factors that influenced the clinicians were their degree of commitment to the trial, their understanding of the scientific background to the trial, time factors, confidence about handling the clinical procedures required, a sense of ownership and good communication with senior staff about the trial. The more junior doctors identified the need for more support from senior staff, as well as for training.

#### Specific strategies to improve recruitment

There are several reports in the literature of clinical trials and elsewhere where specific strategies implemented to improve recruitment

yielded large changes in recruitment rates. A recent example in clinical trials is that of the ORACLE (Role of Antibiotics in Curtailing Labour and Early Delivery) trial,<sup>17</sup> where the introduction of a number of research midwives had a dramatic effect on subsequent recruitment rates. The use of data from these ‘natural experiments’ may provide particularly useful lessons for the formulation of strategies to counter failing recruitment. A systematic review of trials of strategies to increase recruitment in research studies was recently published in which a total of 18 trials was identified, including a total of 39,516 participants.<sup>18</sup> The effectiveness of six different strategies aimed at participants was evaluated. Seven trials evaluated the effect of providing potential participants with additional information, four examined the relative effectiveness of different consent procedures, three evaluated the effect of prewarning, two the use of incentives, one the effect of using a placebo and one trial evaluated the effect of different types of invitation letter. There were, however, no trials of interventions to improve recruitment in multicentre studies, nor trials on how to ensure that study participation is routinely offered to patients.

### **Lessons from research other than healthcare**

The studies mentioned above have all been conducted within the healthcare environment; however, many other organisations have sought to influence and enrol others. For example, in business some firms have sought to develop long-term, mutually advantageous relationships with partners, customers and clients, often with beneficial results. Indeed, improving interorganisational relationships is so well established that ‘relationship marketing’ and ‘partnering’ are extensively discussed in current business literature. Thus, the application of analytical frameworks from outside the healthcare environment may shed new light on the challenge of recruiting and sustaining trial sites.

### **The commissioned research**

It was against this background that the National Coordinating Centre for Research Methodology (NCCRM) (through funding from both the Department of Health and the MRC) commissioned research to identify the factors that are associated with good and poor recruitment to multicentre trials. Particular emphasis was placed in the commissioning brief on the participation of collaborating researchers.

### **The research project**

Reflecting the commissioning brief, the research project outlined in this monograph aimed to identify the factors associated with good and poor recruitment to multicentre trials, concentrating particularly on the participation of collaborating researchers. It also considered the wider issue of what counts as a successful trial, broadening the debate from recruitment alone.

### **Research approach adopted**

To try to understand the potential factors associated with good and poor recruitment more fully, this project undertook to examine recruitment from a number of different perspectives: a ‘multiple lens’ approach. Multiple lens approaches have been used widely in social science for the examination of complex phenomena, organisations or processes. The concept behind the multiple lens approach is that individual perspectives give interesting insights into the situation or procedure under examination, but implicitly lead us to interpret the issues in distinctive yet partial ways. When taken together, however, they give a much wider and insightful vision of the underlying issues. An example of this approach from the field of organisational behaviour was the research undertaken by Morgan<sup>19</sup> to examine the ways in which organisations function. He viewed organisational behaviour from a number of different perspectives (e.g. from the perspective of organisations as machines, organisms and cultures). These perspectives, when considered individually, gave interesting and different insights into the organisation, but when taken together gave a much wider and more rounded insight into the underlying issues. As recruitment to trials is a complex process, the present authors decided to adopt this multiple lens approach to their investigation.

### **Individual components of the research**

Reflecting this innovative approach, the project, known as STEPS (Strategies for Trials Enrolment and Participation Study), had three distinct components (all of which could stand alone but which, when taken together, might provide insights greater than the sum of the individual parts).

#### ***Part A: An epidemiological review of a cohort of trials funded by the MRC and the NHS HTA Programme***

The aim of this component of the study was to explore documentation held by funders on a cohort of trials. These documents provide a rich description of factors that may influence recruitment to multicentre trials, as progress

towards recruitment targets is explicitly monitored and any problems with recruitment are highlighted, together with any strategies adopted to improve recruitment. The aims were to describe the characteristics of the trials in terms of factors that may affect the success of recruitment (e.g. level of funding, complexity of trial design, involvement of a trials support unit), to describe patterns of recruitment observed; and to describe trialists' reports of factors perceived to be associated with good or poor recruitment (e.g. delays in obtaining funding or ethics approval) and strategies attempted to improve recruitment.

**Part B: Case studies of trials that appeared to have particularly interesting lessons for recruitment**

The aim of this component was to explore in more depth trials that may be considered to be 'exemplars' with regard to recruitment. The aims were to examine these exemplars from a variety of internal perspectives; to consider the impact of the unique conditions of the individual trials on recruitment; and to make comparisons across trials with regard to a wide range of factors that might affect recruitment.

**Part C: A single, in-depth case study of a large multicentre trial**

The aim of this component was to examine, in a single ongoing multicentre trial [the MRC Corticosteroid Randomisation After Significant Head Injury (CRASH) trial], the feasibility of applying a business-orientated analytical framework to trial recruitment (i.e. if the trial were a business, what policies, practices and capabilities would be needed for the marketing challenges to be met). The aim was to develop a reference model for potential use in future trials.

**The STEPS group**

The research in the STEPS project was undertaken by a collaborative group, the majority of whose

members had significant experience of conducting large multicentre RCTs. The group was multidisciplinary in background, including trial managers, epidemiologists, statisticians and social scientists. Although separate components of the research were each led by a subgroup of the collaboration (Part A: AM, RK, MC, AG; Part B: CS, JG, DE; Part C: DF, IR), the STEPS group met on several occasions to discuss the work in progress as a whole, and all contributed to the whole project.

**Outline of report**

Reflecting the aims and objectives outlined above, *Chapter 2* describes the epidemiological review of trials funded by the MRC and HTA Programme. An epidemiological description of the cohort of trials is outlined together with the exploration of specific hypotheses of factors that may affect recruitment. *Chapter 3* describes the results of four case studies (two funded by the MRC and two funded by the HTA Programme) of trials that were deemed to have particularly interesting lessons for recruitment. The synthesis of interviews integrating the perspectives of a number of different trial members [e.g. the principal investigator (PI), the trial manager or equivalent, the lead clinical investigator, and other clinicians involved directly in recruiting at local centres] is described. *Chapter 4* describes the application of a business-orientated analytical framework to the MRC CRASH trial. A reference model that could be used to assess the sales and marketing capability of a trial is proposed. In *Chapter 5* the project is discussed as a whole, finishing with recommendations for practice and for further research.





## Chapter 2

# An epidemiological review of a cohort of trials funded by the MRC and the NHS HTA programme

### Background

For every trial funded by the UK MRC and the UK NHS HTA Programme, the PI and co-applicants must initially submit a full scientific application to the funder outlining the rationale for the trial, the required sample size and the expected recruitment rate. Once the trial is underway, regular progress reports, annually for MRC trials and 6-monthly for HTA Programme trials, must be submitted to the funder outlining the progress of the trial against the original timeline and expected milestones. Within these reports, progress against recruitment targets is explicitly monitored and any problems with recruitment are highlighted, together with any strategies adopted to improve recruitment. If further funding or an extension in time, or both, is requested, a formal application is made. The application and reporting documents submitted by trial teams to funders provide a rich description of recruitment to multicentre trials and factors that may influence recruitment.

This component of the project aimed to draw on these documents to describe recruitment to a cohort of multicentre trials funded by the MRC and the HTA Programme, and to explore factors that may have influenced good or poor recruitment.

### Aims

The specific aims and objectives of this component of the research were:

- to describe the trials in terms of broad study characteristics such as population, intervention and outcomes
- to describe patterns of recruitment observed such as to original plan or better, slower start than anticipated, recruitment with identifiable change-points, etc.
- to characterise the trials in terms of factors that might affect the success of recruitment, such as level of funding, complexity of trial design or involvement of a trials support unit
- to describe trialists' reports of factors perceived to be associated with good or poor recruitment (e.g. delays in obtaining funding or ethics approval) and strategies attempted to improve recruitment
- to consider any changes in overall recruitment pattern over time (based on year in which recruitment commenced).

### Methods

#### Identification of trials

Trials were identified from the databases of trials held by the two funding bodies. Trials were deemed eligible for inclusion in the study if:

- they involved more than one clinical centre;
- recruitment to the trial started on or after 1 January 1994 (this cut-off was chosen as the HTA Programme was established during 1993); and
- the planned end-of-recruitment date (as in application/first protocol) occurred on or before 31 December 2002. Trials where the intention was that recruitment would close by 31 December 2002, but were later awarded an extension to the recruitment phase beyond 31 December 2002, were included (if they had subsequently closed to recruitment prior to data extraction).

Trials were specifically excluded from this study if they had adopted a cluster randomised design. Recruitment issues are different for cluster RCTs as often individual participants are not approached for consent, rather consent is given for specific clusters of participants by a cluster 'guardian'.<sup>20</sup> It was, therefore, felt that reasons for good or poor recruitment would be systematically different between individually randomised and cluster randomised trials.

#### Deviations from the original plan of work set out in the application form

The original intention was to include multicentre trials funded from 1997 onwards (when the MRC reporting structure began). It became evident that

this would not generate an adequate number of trials in the cohort. The inclusion criteria were thus amended to include multicentre trials that started recruitment on or after 1 January 1994 (this cut-off was chosen as the HTA Programme was established during 1993).

### **Access to information**

Following discussions with staff at MRC and the National Coordinating Centre for the HTA Programme (NCCHTA), it was agreed that the study researchers would be given access to application forms and progress report details on site at each organisation, subject to appropriate confidentiality safeguards. The structure of current progress reports is outlined in Appendix 1. Researchers signed confidentiality agreements at both sites. The MRC and HTA Programme contacted all nominated PIs by letter before the records for their project were reviewed. It was agreed that any material deemed confidential or of a sensitive nature that made it irrelevant or inappropriate to the data extraction exercise would be removed before the files were passed to the researchers. This did not prove necessary in practice.

### **Data extraction**

Data were extracted from trial reports under six structured headings:

- trial identifying details
- trial administrative details (e.g. date of application submission, date funding commenced, date ethics approval received, date recruitment commenced)
- trial features (e.g. did the trial have a pilot phase, were the trial team multidisciplinary, was there a dedicated trial manager, were consumers involved, trial design, trial setting)
- finance (i.e. overall funding awarded together with any supplementary awards provided)
- summary of overall recruitment, including original recruitment target (sample size sought in specified period as stated in the grant application), any revisions to recruitment targets, and final recruitment numbers
- description of components of delay or failure to reach recruitment target, including factors such as delays to centre recruitment, delays to participant recruitment and any strategies adopted to attempt to improve recruitment.

The data extraction form (Appendix 2) and procedures were piloted on data from eight trials funded by the HTA Programme (data from these trials were also subsequently formally extracted

using the finalised data extraction form). This enabled the process and contents of the data extraction form to be refined. Two researchers (RK, AM) performed the data extraction (each extracted information from both MRC trials and HTA Programme trials). For the first few trials, the researchers worked together on the data extraction, to agree working rules for the definition and classification of terms. Following this, formal definitions of terms (e.g. definition of multidisciplinary input) were developed to aid the standardisation of data extraction and are presented in Appendix 3.

### **Secondary data sources**

For some data items, information was not recorded or was unclear in some trial reports held by the funders. In such situations, reports of the specific trials held on the Current Controlled Trials meta-register of randomised trials ([www.controlled-trials.com](http://www.controlled-trials.com)) and the NCCHTA website ([www.ncchta.org](http://www.ncchta.org)) were also searched in an attempt to augment the dataset. The Current Controlled Trials meta-register is an international database combining several registers of ongoing clinical trials and includes registers of UK-funded trials (e.g. National Research Register). For some trials, PIs were also asked to provide additional information. To avoid overloading PIs, especially for information about trials that had long since closed, contact was only made when a 'core' item of data, such as the final recruitment figure, was missing.

### **Analysis**

#### **Classification of recruitment 'success'**

Recruitment was classified as 'successful' if a trial recruited to or over 100% of its original target, irrespective of time-frame. Further analyses were based on trials that recruited at least 80% of their original recruitment target. A sensitivity analysis was performed, treating trials that stopped early owing to differential effects as having had successful recruitment.

#### **Generation of a priori research hypotheses of factors that might affect recruitment**

To protect against being data driven in the exploration of factors that might affect recruitment, a number of a priori hypotheses to be tested was developed. These hypotheses were generated within the project management group and were based on issues raised in previous literature reviews<sup>5</sup> and insights gained from the MRC clinical trials enquiry<sup>4</sup> (AG and IR were both members of the main review panel of the MRC clinical trials enquiry). The specific hypotheses were that:

- Trials with complex designs (more complex than a parallel group trial, e.g. factorial trials) do not recruit as well as simple trials.
- Less well funded trials do not recruit well (this was initially operationalised as trials with less than £500,000 funding, but subsequently operationalised as trials with less than £1000 per planned participant).
- Trials without dedicated trial management expertise do not recruit as well as those with trial management expertise (defined as a person responsible for the day-to-day coordination).
- Trials with multidisciplinary input recruit better than those that do not have this input.
- Trials that involve consumers recruit better than those that do not.
- Trials where the intervention is only available inside the trial recruit better than those where the intervention is available outside the trial.
- Trials that have had a successful pilot phase (defined as either a pilot or feasibility study that addressed anything to do with recruitment, including changes to trial documentation) recruit better than those that do not have a pilot phase.
- Trials that have dedicated, paid local coordinators recruit better than those that do not.
- Cancer trials recruit better than non-cancer trials.
- Drug trials recruit better than non-drug trials.
- Trials funded through response-mode funding have different recruitment rates to those funded through a commissioned process.

### Statistical analysis

Data were collated and stored in a specially created database (MS Access, version 2000) and analyses were performed using SPSS (version 11). Frequency tables were generated to summarise the overall trial characteristics. Associations between trial characteristics and recruitment success were generated through the use of  $2 \times 2$  tables. Odds ratios (ORs) of recruitment success are presented together with 95% confidence intervals (CIs). Statistical levels of association were examined through the use of the  $\chi^2$  test, or the  $\chi^2$  test for trend where appropriate.

## Results

### Description of included trials

#### Summary of included trials

One-hundred and fourteen trial grants fulfilled the inclusion criteria. Forty-one (36%) of these

trials were funded through the HTA Programme and the remaining 73 (64%) trials funded by the MRC. Some of the trial grants supported more than one trial: three grants included two subtrials, one grant had three subtrials and one trial grant had four subtrials. For the purposes of describing the trial features, the denominator is based on the number of trial grants (i.e. 114), whereas for the analysis of recruitment issues the denominator is based on all trials (including subtrials) (i.e. 122 trials).

### Trial design

Trial designs are summarised in *Table 1*. Across all trials (including the eight subtrials) the large majority were simple parallel group trials (113/122, 93%). Six trials adopted a factorial design, and another three adopted a partially randomised, patient preference approach.

The majority were two-arm (93/122, 76%) trials. There were 18 (15%) three-arm trials and 12 (9%) trials with more than three-arms (factorial trials are coded here as multiarm trials; for example a  $2 \times 2$  factorial would be a four-arm trial under this coding).

### Trial setting

A wide range of clinical areas was covered (*Table 2*). Cancer trials accounted for 20% of the total. Mental health and orthopaedics/rheumatology each accounted for a further 17% of the total. Obstetrics and gynaecology also accounted for a sizeable percentage of the trials (7%).

Approximately half (64/122, 53%) of the trials were based in a hospital setting. A further 21% were based in a general practice setting, 6% in a community setting and 13% in a mixed setting (*Table 2*). Across these different settings, just over half (52%) involved recruiting centres that were geographically spread out over a number of regions. Twenty-five (22%) trials involved recruiting centres that were outside the UK.

### Trial interventions

Trial interventions are summarised in *Table 3*. Nearly one-third of the trials involved drugs

**TABLE 1** Design of Part A trials (N = 122) categories

| Design                                  | n (%)    |
|---|----------|
| Parallel                                | 113 (93) |
| Factorial                               | 6 (5)    |
| Partially randomised patient preference | 3 (2)    |

**TABLE 2** Setting of Part A trials

|   | <b>N</b> | <b>n (%)</b> |
|---|----------|--------------|
| <i>Clinical areas</i>   | 122      |              |
| Cancer  |          | 25 (20.5)    |
| Mental health (including neurosciences/psychiatry/psychology) |          | 21 (17.2)    |
| Orthopaedics/rheumatology (including back pain)               |          | 21 (17.2)    |
| Obstetrics and gynaecology                                    |          | 9 (7.4)      |
| Primary care  |          | 8 (6.6)      |
| Cardiology  |          | 5 (4.1)      |
| Gastroenterology  |          | 5 (4.1)      |
| Incontinence/urology  |          | 5 (4.1)      |
| HIV/AIDS  |          | 5 (4.1)      |
| Vascular  |          | 4 (3.3)      |
| Minor surgery   |          | 3 (2.5)      |
| Respiratory disease   |          | 3 (2.5)      |
| Dermatology   |          | 2 (1.6)      |
| Dental  |          | 2 (1.6)      |
| Gerontology   |          | 1 (0.8)      |
| Cerebrovascular   |          | 1 (0.8)      |
| Hearing research  |          | 1 (0.8)      |
| Ophthalmology   |          | 1 (0.8)      |
| <i>Setting</i>  | 122      |              |
| Community   |          | 7 (5.7)      |
| General practice  |          | 26 (21.3)    |
| Hospital  |          | 64 (52.5)    |
| Mixed   |          | 16 (13.1)    |
| Missing   |          | 9 (7.4)      |
| <i>Geographical spread</i>                                    | 122      |              |
| Regional  |          | 51 (41.8)    |
| Multiple regions  |          | 63 (51.6)    |
| Missing   |          | 8 (6.6)      |
| <i>Any recruiting centres outside UK</i>                      | 114      |              |
| Yes   |          | 25 (22.0)    |
| No  |          | 88 (77.2)    |
| Missing   |          | 1 (0.8)      |

(excluding chemotherapy) (37/122, 30%). There were 12 (10%) trials in which the intervention was based on a form of behavioural therapy. Chemotherapy, different types of surgical interventions, new service provision and radiology also accounted for sizeable percentages of the interventions.

For the majority of trials (77%), trial interventions were available outside the study; for only 18 trials was it clear that one or more interventions were not available outside the trial.

### **Trial funding**

Trial funding ranged from £16 per planned participant to £4522, with a median of £641 per planned participant. Trial funding was classified as 'good' if applicants were awarded more than £1000 per planned participant for the conduct of

the trial. Using this assumption, 24 (24/89, 27%) trials were awarded a 'good' level of funding.

### **Pilot phase**

Sixty (53%) trials had a pilot phase, of which 58% (35/60) were funded pilots (Table 4). Of these, 32 trials indicated that the recruitment strategy was changed as a result of the pilot study. The most common changes noted on the basis of pilot studies were that written trial materials were modified (eight trials), the trial design was changed (six trials), changes were made to the inclusion criteria (four trials), the recruitment target was changed (six trials), and the number of sites was increased (four trials).

### **Trial coordination and disciplinary representation**

Eighty-nine (78%) trials were coordinated from a trials support unit and 86 (75%) trials had a

**TABLE 3** Interventions in Part A trials (N = 122)

|  | n (%)     |
|--|-----------|
| Medical (drugs, including chemotherapy)  | 47 (38.5) |
| Behavioural therapies (e.g. CBT with or without conventional drugs)              | 12 (9.8)  |
| Different types of surgical intervention (including laparoscopic)                | 12 (9.8)  |
| New services/treatment policy/information provision (e.g. support programmes)    | 9 (7.4)   |
| Radiology (including ultrasound)   | 8 (6.6)   |
| Medical instruments (e.g. metal stents, pacemakers, bandage types)               | 7 (5.7)   |
| Surgery versus alternative (e.g. conservative management, radiotherapy)          | 4 (3.3)   |
| Alternative therapies (including complementary medicines, water-based therapies) | 4 (3.3)   |
| Radiotherapy and/versus chemotherapy   | 3 (2.5)   |
| Radiotherapy   | 3 (2.5)   |
| Physiotherapy  | 3 (2.5)   |
| Anaesthesia/ventilation  | 3 (2.5)   |
| Pharmacy-led reviews/repeat prescribing  | 2 (1.6)   |
| Best management of a medical situation   | 2 (1.6)   |
| Surgery: primary care versus secondary care                                      | 1 (0.8)   |
| Telemedicine   | 1 (0.8)   |
| Management in primary care versus secondary care                                 | 1 (0.8)   |

CBT, cognitive behaviour therapy.

**TABLE 4** Descriptive features of Part A trials (N = 114)

| Trial feature   | Yes<br>n (%) | No<br>n (%) | Not known<br>n (%) |
|---|--------------|-------------|--------------------|
| Trial had pilot study   | 60 (53)      | 41 (36)     | 13 (11)            |
| Was pilot funded? (N = 60)  | 35 (58)      | 4 (7)       | 21 (35)            |
| Was there a change in recruitment strategy because of pilot study? (N = 60) | 32 (53)      | 5 (8)       | 23 (39)            |
| Trial coordinated from trials unit  | 89 (78)      | 25 (22)     | –                  |
| Trial had dedicated trial manager   | 86 (75)      | 14 (12)     | 14 (12)            |
| Trial had paid local staff available  | 61 (54)      | 31 (27)     | 22 (19)            |

dedicated trial manager (Table 4). Seventy-five (75/86, 87%) of those trials with a dedicated trial manager were coordinated from a trials unit. Ninety-two per cent (104/113) of trials had multidisciplinary involvement (defined as medical/dental/nursing expertise plus at least one other discipline) across the trial applicants (Table 5), with statistics (73%) and economics (58%) the highest represented disciplines after clinical expertise.

Nine trials indicated that they had some form of consumer involvement, although no trial had a consumer as a grant applicant. Trialists most commonly identified that they had access to appropriate consumer bodies/patients with the relevant condition (five trials), although in some cases specific roles for the consumer were noted: representation on the trial steering committee (one trial), reviewer of trial literature (one trial) and referee of the final report (one trial).

## Recruitment in included trials

### Summary of overall recruitment

Recruitment target varied widely across trials, from a minimum of 60 to a maximum of 66,000.

Recruitment in the trials is summarised in Table 6.

Thirty-eight (31%) trials were assessed to have recruited 'successfully' (i.e.  $\geq 100\%$  of their original target). A further 29 (24%) of trials achieved a recruitment rate of at least 80% but less than 100% of their original target. Thirteen trials recruited to their original target after a time extension. Fifty-five (45%) trials recruited below 80% of their original recruitment target. In 42 (34%) trials the recruitment target was revised over the course of the trial. The target was revised in an upward direction in six of these trials. Of the 42 trials that revised their target, 19 (45%) recruited 100% or more of their revised target, 15 (36%) trials recruited at least 80% but less than 100% of revised target, and eight trials did not achieve even 80% of the revised target. Six trials recruited

**TABLE 5** Disciplines represented amongst trial investigators listed as applicants in Part A trials (N = 113<sup>a</sup>)

|   | Yes<br>n (%) | No<br>n (%) |
|---|--------------|-------------|
| Multidisciplinary                             | 104 (92)     | 9 (8)       |
| <i>Disciplines represented</i>                |              |             |
| Consumer                                      | –            | 113 (100)   |
| Economics                                     | 66 (58)      | 47 (42)     |
| Health Services Research                      | 35 (31)      | 78 (69)     |
| Medical/dental                                | 109 (96)     | 4 (3)       |
| Nursing                                       | 22 (19)      | 91 (80)     |
| Statistics                                    | 83 (73)      | 30 (26)     |
| Other   | 17 (15)      | 96 (85)     |
| <sup>a</sup> Data were missing for one trial. |              |             |

**TABLE 6** Recruitment in Part A trials (N = 122)

|  | n (%)     |
|--|-----------|
| <b>Recruited successfully</b>          |           |
| Yes                                    | 38 (31.1) |
| No                                     | 84 (68.9) |
| <b>Was recruitment target revised?</b> |           |
| Yes                                    | 42 (34.4) |
| No                                     | 76 (62.3) |
| Missing                                | 4 (3.3)   |
| <b>Final recruitment figure</b>        |           |
| <i>Original target (N = 122)</i>       |           |
| ≥100%                                  | 38 (31.1) |
| ≥80% but <100%                         | 29 (23.8) |
| <80%                                   | 55 (45.1) |
| <i>Revised target (N = 122)</i>        |           |
| ≥100%                                  | 19 (45.2) |
| ≥80% but <100%                         | 15 (35.7) |
| <80%                                   | 8 (19.1)  |

to their revised target within the original time-frame. Enrolment was halted before the formal end of the recruitment period in 14 trials. In 11 of these, this decision was related to poor recruitment. In the three others, early termination followed a recommendation from a data monitoring committee (DMC) that there were clear differences between the trial groups. However, in two of these, the recruitment period had already been extended beyond that originally specified.

**Extensions to trials**

Sixty-six (54%) trials requested an extension to the trial grant to complete the original trial; in all but one of the cases either a time-only

**TABLE 7** Delays to different stages of recruitment in Part A trials

|   | N   | n (%)     |
|---|-----|-----------|
| <i>Overall start to recruitment delayed</i>               |     |           |
| Yes   | 114 | 47 (41.2) |
| No  |     | 64 (56.1) |
| Missing   |     | 3 (2.6)   |
| <i>Early participant recruitment slower than expected</i> |     |           |
| Yes   | 122 | 77 (63.1) |
| No  |     | 35 (28.7) |
| Missing/not clear   |     | 10 (8.2)  |
| <i>Late participant recruitment slower than expected</i>  |     |           |
| Yes   | 122 | 46 (37.7) |
| No  |     | 60 (49.2) |
| Missing/not clear   |     | 16 (13.1) |

extension or a supplementary grant was awarded. Where an extension was awarded, in 42 (64%) cases this was for both a time extension and a supplementary grant. For the remainder, 15 (23%) were for a time-only extension and eight (12%) were for a supplementary grant only. Only 19 (45%) trials whose targets were revised were known to have successfully recruited to their new target.

**Delays at different phases of recruitment**

**Delay to overall start of recruitment**

In 47 (41%) trials, the overall start to the recruitment was delayed (Table 7). The main reasons cited were: delays related to central trial staff (11 trials), delays related to local research staff (11 trials) and delays related to local clinical arrangements (seven trials) (Table 8). Other reasons identified included a range of issues, such as delays with ethics, the supply of study drugs/placebo, the development of clinical guidelines, which then impacted on the trial, the PI moving, adverse publicity about research and the publishing of conflicting research (Table 8).

**Recruitment of centres**

Eighty-six (75%) trials indicated that they had preidentified centres in the application for inclusion to the trial. In 17 of these, however, there was some level of failure in bringing in some of the preplanned centres (Table 9). There appeared to be no common reason for these failures, although the issue of problems with time delays resulting in technology advances was identified (three trials), as were cost issues (raised in two cases).

**TABLE 8** Reasons for delays to overall start of recruitment (N = 47<sup>a</sup>)

|   | <i>n</i> |
|---|----------|
| Central staff   | 11       |
| Local research staff  | 11       |
| Local clinical arrangements:  | 7        |
| Merging/reorganisation of trusts  | 2        |
| Concern that workload and costs would increase as patients with the condition would be identified and would require treatment   | 1        |
| Problems with implementation as clinic visit did not facilitate discussing trial participation  | 1        |
| Major relocation of services  | 1        |
| Centres did not have experience in skin testing   | 1        |
| Indemnity   | 1        |
| Funding issues  | 6        |
| MREC  | 5        |
| LREC  | 5        |
| Supply of drugs/placebo (including costs/supply)  | 4        |
| R&D   | 1        |
| Development of evidence-based guidelines took longer than anticipated   | 1        |
| Adverse publicity about medical research  | 1        |
| Administrative delays   | 1        |
| Clarification about information to be collected for health economics  | 1        |
| Setting up GP practices took longer than anticipated: many extra practices in each region had to be recruited   | 1        |
| Simultaneous other local research projects  | 1        |
| Lack of national service framework in disease area  | 1        |
| Delay new IM&T strategy for the NHS in England 'Information for Health' as team aspired to use the NHS-wide network as the means of data transmission   | 1        |
| Had anticipated starting at a major holiday period (Christmas)  | 1        |
| Contract agreement between university and trust   | 1        |
| Following pilot, discussions on changing trial design   | 1        |
| Changes in data legislation resulted in delay in mailing prospective participants   | 1        |
| In a fast-moving field, technical aspects included in initial proposal had to be revisited to ensure that the most appropriate technology available was being used  | 1        |
| <sup>a</sup> More than one reason for an overall delay to start of recruitment was reported by several trials. IM&T, Information Management and Technology; LREC, local research ethics committee; MREC, multicentre research ethics committee. |          |

**TABLE 9** Reasons why trials failed to sign up some of the preidentified centres (N = 17)

|  | <i>n</i> |
|--|----------|
| No specific reasons for failure recorded in reports  | 4        |
| Technologies/techniques had moved on, resulting in changing views about treatment (in at least one case this was due to time delay between application and recruitment starting) | 3        |
| Local staff issues/changes/shortages   | 2        |
| Support costs (lengthy process of applying for Culyer funding resulted in some surgeons not participating in one trial)  | 2        |
| Equipoise (problems with recruiting fully cooperating multidisciplinary teams willing to randomise patients between at least two of the management policies)                     | 2        |
| Complete change in trial base (PI moved)   | 1        |
| Changed end-point (brought forward), which meant that some sites never started   | 1        |
| Costs (of intervention)  | 1        |
| Costs (could not compete with commercial studies in same disease area)   | 1        |

**TABLE 10** Reasons for early participant recruitment problems (N = 77<sup>a</sup>)

|   | <b>n</b> |
|---|----------|
| Fewer eligible than expected  | 19       |
| Internal problem (e.g. staff)   | 18       |
| Smaller percentage agreeing to participate  | 16       |
| Eligible people missed  | 10       |
| External problem (e.g. publicity)   | 8        |
| Funding (e.g. payment to sites considered too low, cost of intervention)                    | 5        |
| Issues with procedures/interventions (e.g. length of recruitment procedure, use of placebo) | 5        |
| Absence of perceived clinical equipoise   | 4        |
| Complexity of trial/design/materials  | 4        |
| Changing referral patterns  | 3        |
| Competing research  | 3        |
| Conflicting workload pressures  | 3        |
| Long waiting lists  | 2        |
| Time delay since grant application (treatment for condition had changed)                    | 2        |
| Service support/treatment costs   | 2        |
| Recruitment started during major holiday period   | 1        |
| Local restrictions on use of intervention   | 1        |
| No perceived individual gain to justify participation                                       | 1        |
| Service pressures   | 1        |
| LREC delays   | 1        |
| Problems with supply of intervention  | 1        |
| Language/written English difficulties   | 1        |
| Introduction of internal market   | 1        |
| Trial process too demanding   | 1        |

<sup>a</sup> More than one reason for early recruitment problems was reported by several trials.

Similarly, 37 (32%) trials indicated that they encountered some form of delay in bringing in some of the preidentified centres. As before, reasons for this varied. The most commonly reported reasons included problems with costs/funding (13 trials), delays in the recruitment of research staff (12 trials) and changes with the MREC system (six trials).

Fifty-two (45%) trials reported that they had to recruit new centres to ensure the delivery of the trial.

#### **‘Early’ participant recruitment**

Once centres were enrolled into the trials, early (within the first approximately 25% of recruiting time) recruitment was reported to be slower than anticipated in 77 (63%) trials (*Table 7*). The most common reasons noted for this are outlined in *Table 10*, and included fewer eligible patients than expected (19 trials), internal problems (e.g. staff) (18 trials) and a smaller percentage of patients agreeing to participate than expected (16 trials). Other problems included: issues with procedures/interventions (e.g. randomisation, placebo (five trials), the absence of perceived clinical equipoise (four trials) and conflicting workload pressures (three trials).

#### **‘Later’ participant recruitment**

There were also delays to later (within the last approximately 75% of recruiting time) recruitment reported in 46 (38%) trials (*Table 7*). The most common reasons noted in this phase (outlined in *Table 11*) were internal problems (e.g. staff) (ten trials), a smaller percentage of patients agreeing to participate than expected (nine trials), and fewer eligible patients than expected (seven trials). Other problems were numerous, and included issues such as conflicts with other trials (five trials) and long waiting lists (three trials).

#### **Recruitment rates related to year recruitment started**

Data describing recruitment rates for all years when recruitment started are summarised in *Figure 1*. Six of the 15 trials (40%) that commenced recruitment in 1994 recruited at least 100% of their original recruitment target. Lower proportions of trials achieved their targets among those begun in the late 1990s.

#### **Association between trial features and recruitment ‘success’**

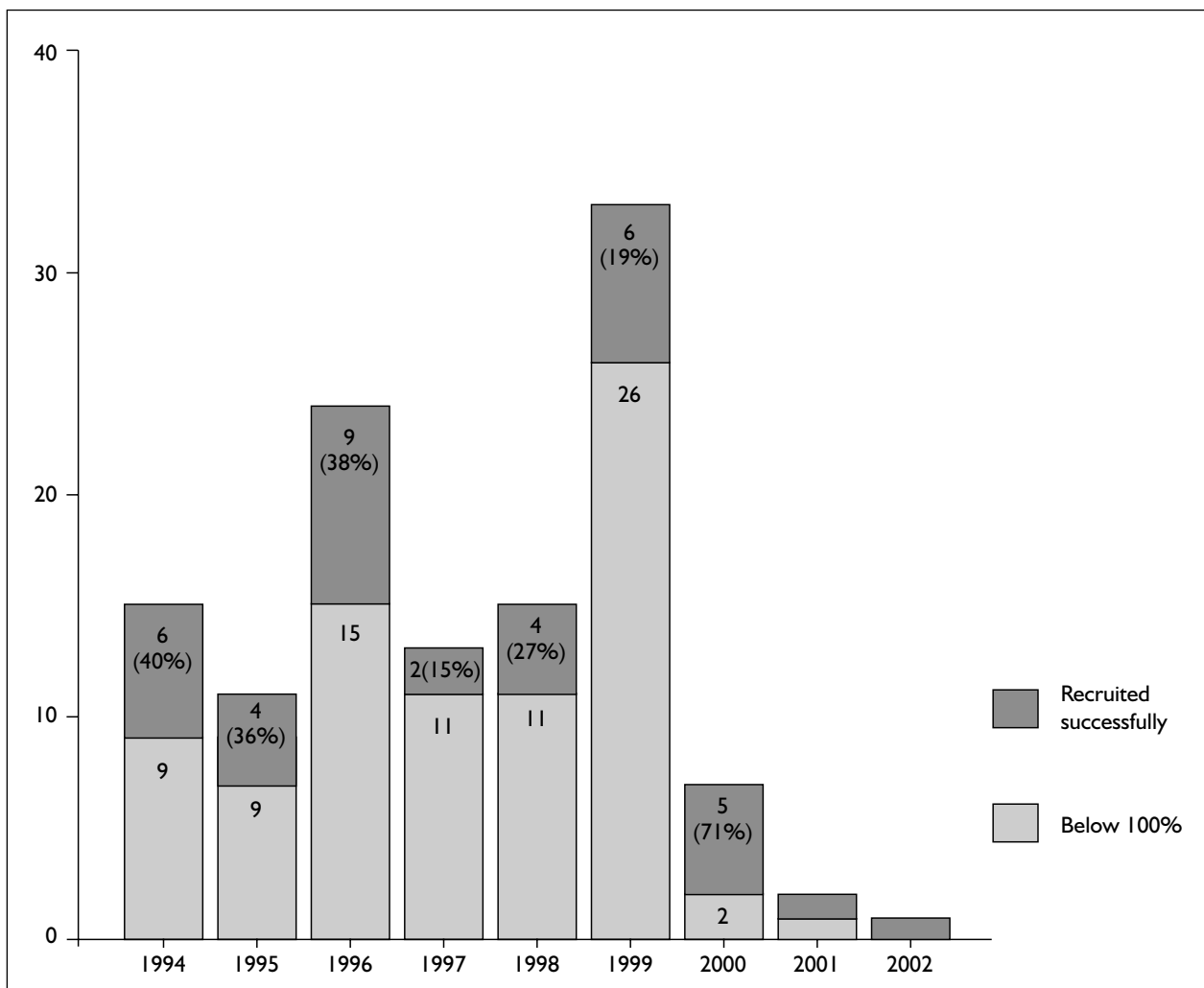
As indicated above, 38 (31%) trials were deemed to have recruited successfully (i.e.  $\geq 100\%$  of the original recruitment target). Potential relationships



**TABLE 11** Reasons for late participant recruitment problems (N = 46<sup>a</sup>)

|  | <i>n</i> |
|--|----------|
| Internal problem (e.g. staff)  | 10       |
| Smaller percentage agreeing to participate   | 9        |
| Fewer eligible than expected   | 7        |
| External problem (e.g. publicity)  | 7        |
| Funding difficulties (including payment to local investigators considered too low, problems with funding intervention) | 5        |
| Conflict with other trials   | 5        |
| Long waiting lists   | 3        |
| Treatment preferences  | 2        |
| Eligible people missed   | 1        |
| Department policies  | 1        |
| Recruitment targets too ambitious  | 1        |
| Trial fatigue  | 1        |
| No local access to intervention  | 1        |
| Trial methodology considered too complex   | 1        |
| Delays in LREC approval  | 1        |
| Decline in surgical procedures   | 1        |
| Problems with R&D approval   | 1        |
| Research not considered a priority by GPs (no career incentive)  | 1        |
| Additional theatre time required   | 1        |

<sup>a</sup> More than one reason for late recruitment problems was reported by several trials.



**FIGURE 1** Recruitment success related to start year in Part A trials

**TABLE 12** Associations between features of Part A trials and recruitment success

| Feature                                       | Valid N | No. with feature that had successful <sup>a</sup> recruitment<br>n (%) | No. that did not have feature that had successful <sup>a</sup> recruitment<br>n (%) | OR   | 95% CI        | p-Value |
|---|---------|--|---|------|---------------|---------|
| Simple design                                 | 122     | 35/116 (30)  | 3/6 (50)  | 0.43 | 0.06 to 3.41  | 0.374   |
| Good level of funding                         | 89      | 7/24 (29)  | 17/65 (26)  | 1.16 | 0.41 to 3.29  | 0.776   |
| Multidisciplinary input                       | 113     | 34/104 (33)  | 3/9 (33)  | 0.97 | 0.19 to 6.36  | 0.615   |
| Consumer input                                | 107     | 4/9 (44)   | 26/91 (29)  | 2.00 | 0.36 to 10.05 | 0.446   |
| Interventions only available inside the trial | 112     | 7/18 (39)  | 26/94 (28)  | 1.66 | 0.58 to 4.76  | 0.338   |
| Pilot phase                                   | 109     | 18/66 (27)   | 11/43 (26)  | 1.09 | 0.46 to 2.61  | 0.845   |
| Dedicated trial manager                       | 107     | 32/91 (35)   | 2/16 (13)   | 3.80 | 0.79 to 36.14 | 0.087   |
| Local recruitment coordinators                | 100     | 15/69 (22)   | 14/31 (45)  | 0.34 | 0.14 to 0.84  | 0.017   |
| Support from a trials unit                    | 122     | 27/94 (29)   | 11/28 (39)  | 0.62 | 0.26 to 1.50  | 0.289   |
| Cancer trial                                  | 122     | 12/24 (50)   | 26/98 (27)  | 2.77 | 1.11 to 6.93  | 0.026   |
| Drug trial                                    | 122     | 19/53 (36)   | 19/69 (28)  | 1.47 | 0.68 to 3.18  | 0.326   |
| Funded by the MRC                             | 122     | 28/74 (38)   | 10/48 (21)  | 2.31 | 1.00 to 5.36  | 0.048   |

<sup>a</sup> ≥ 100% original target.

between trial features that were prespecified as likely to enhance the chances of successful recruitment are presented in *Table 12*. An association suggesting that the factor increased the chances of successful recruitment is indicated by an odds ratio of greater than unity. For each comparison, only trials for which the information was known were included (i.e. trials where the information was unclear or missing were excluded). Subtrials were included. Ninety-five per cent confidence intervals are presented for all odds ratios.

As *Table 12* shows, the confidence intervals around the odds ratio estimates were all wide, reflecting the maximum sample size (122). Some of the comparison cells had very few data (e.g. number with a complex design and number with consumer input). There were marginally statistically significant associations with being funded by the MRC, being a cancer trial and not having paid local trial coordinators.

### Strategies to improve recruitment

Seventy-three trials reported the use of at least one strategy (range one to five strategies) aimed at improving recruitment (*Table 13*). A variety of strategies was reported; the most commonly reported strategy was the use of newsletters and mailshots, both to participants and to clinical staff, to promote the trial. There were reports of advertisements in newspapers and journals. Posters and information leaflets were displayed in

appropriate clinics and wards and these were sometimes backed up by regular phone calls and visits. Several trials reported that sites had been supplied with resource manuals and that specific training had been held for staff recruiting patients. Another commonly reported strategy was the trial being presented to appropriate clinical groups and presentations at relevant national and international meetings. Ten per cent of the trials reported that the trial inclusion criteria were changed or the protocol was amended in an effort to improve recruitment. Less commonly reported strategies included provision of training videos for sites and appropriate special interest groups being asked to inform patients about the study.

### Specific recruitment patterns

Trials were examined for any identifiable change-points in recruitment. Unfortunately, no trial was found to display particularly marked changes in recruitment rates and no analyses based on specific recruitment patterns were possible.

### Discussion

This description of a complete historical cohort of trials has shown that failure to achieve projected targets for participant recruitment has been common in multicentre trials supported by the two main funders of trials in the UK. Well over half failed to recruit to 100% or more of their original target, and 45% failed to recruit to within 80% of

**TABLE 13** Reported strategies aiming to improve recruitment in Part A trials (N = 73)

|   | No. of trials |
|---|---------------|
| <i>Number of strategies reported</i>  |               |
| 1   | 25            |
| 2   | 29            |
| 3   | 12            |
| 4   | 6             |
| 5   | 1             |
| <i>Types of recruitment strategy adopted</i>  |               |
| Newsletters/mailshots/flyers (to participants and/or clinical staff)  | 26            |
| Regular visits/telephone calls to wards/sites/practices   | 15            |
| Posters/information leaflets in clinics/wards/notes   | 13            |
| Inclusion criteria changed/protocol amended   | 12            |
| Presentations to appropriate groups (e.g. at consultant meetings, community-based physiotherapists)   | 10            |
| Resource manual for site staff/trained staff in disease area/procedures being investigated/role-play exercises/study day/workshops for recruiters | 10            |
| Advertisement/articles in newspapers/journals; radio interviews   | 8             |
| Presentations at national/international meetings  | 6             |
| Employed extra staff  | 6             |
| Investigators' meetings/recruiting staff meetings   | 5             |
| Training/information videos   | 4             |
| Incentives for recruiters (e.g. prize draw, chocolates)   | 4             |
| Trial material revised/simplified/customised for specific sites   | 4             |
| Visits to centres by PIs/senior members of study group  | 3             |
| Repeated contact by telephone/letter to individuals/sites   | 3             |
| Increased/changed time-points when information provided to potential participants   | 3             |
| Supportive statements from opinion leaders  | 3             |
| Merchandise/desktop reminders with trial logo for site staff  | 2             |
| Website information   | 2             |
| Special interest groups (e.g. physiotherapists interest group), asked to publish information about study and request referrals                    | 2             |
| Use of hospital system to identify potential participants   | 2             |
| Simplified process of payment   | 1             |
| Paid incentive to participants  | 1             |
| Protected time for site staff   | 1             |
| Randomisation procedures changed  | 1             |
| Resources for recruiting staff increased in sites that were recruiting well and reduced in those that were not                                    | 1             |
| Initial check for eligibility over telephone  | 1             |
| Focus groups  | 1             |
| Interpreters available  | 1             |
| Complete review of recruitment procedures   | 1             |
| Industry supplied or discounted cost of trial intervention  | 1             |
| Experienced trial manager enrolled to help with design of promotion material and drive the trial  | 1             |

the original target. For around half of the trials the recruitment period was extended, usually supported by a supplementary grant. Reasons varied, but delays were experienced at all stages. Some trials experienced delays to starting recruitment; many had delays during recruitment, both during the early phase and later once the trial had been established. Analyses to explore factors that it was thought in advance might be associated with successful recruitment were relatively uninformative. The confidence intervals around the estimated odds ratios were all wide and too imprecise to allow judgement about possible causal relationships.

The strength of the study was that it included a systematically identified, complete cohort of trials funded by the two major UK public funding bodies in the field of healthcare and drew on previously confidential routine progress reports submitted over the course of a trial by the investigators. The large majority of trials were parallel group trials, with only a small number of trials with more complex designs. The trials represented a wide spectrum of clinical areas, clinical settings and geographical centres. Cancer trials and drug trials were most commonly represented. This is therefore a thorough description of the progress of multicentre trials

over time, and of the extent of the problem of under-recruitment to trials.

The study does have weaknesses, however. The basis of the investigation was that the 'outcome' of recruitment to a predefined target (original sample size estimate) is a true measure of success. Often initial sample size calculations are based on limited information and, as such, the use of this marker as a sole indicator of recruitment success is rather unsatisfactory. Initial sample size estimates can be viewed more as an informed guide, based on imperfect information (that may change as new information emerges from external sources) and considerations such as feasibility and cost. Sample size targets do, however, contribute to the decision-making process when funding decisions are made and, as such, the degree to which a trial delivers to initial expectations can be viewed as a legitimate marker of trial success. In an ideal situation, parameters other than achievement of planned sample size, such as rates of participant retention and treatment compliance, should also be taken into account. Furthermore, recruitment can be viewed as a surrogate measure of other, less easily quantifiable, but arguably more significant measures of success, such as 'impact on clinical practice' or the extent to which the trial question has been successfully addressed. In terms of recruitment, it was anticipated that some of the apparent failure to reach recruitment targets might have been due to a DMC's recommendation to halt the trial. In fact, in only three cases did a DMC recommend closing recruitment because of clear differences in outcome between the trial groups; in two of these, however, there had already been an extension to the recruitment period because the rate had been slower than planned. Sensitivity analyses treating these three as having 'successful recruitment' had little impact on the results, although they did strengthen somewhat the association between success and a trial having a dedicated trial manager.

Another limitation is that the operationalisation of variables used to address the research hypotheses of factors that might affect recruitment (the 'exposures') was based on pragmatic considerations which could not always reflect subtle variations in the underlying concepts. For instance, different trials need quite different levels of funding and the choice of a standard cut-off of £1000 per planned participant was arbitrary.

There are also some worries about the validity of the data. There was marked variation in the quality of the reporting across the 114 studies. This was particularly noticeable between the two funders;

primarily a reflection of the specific requirements of the reporting form. The reporting form for the HTA Programme is more extensive and requires greater detail for correct completion. It is also completed 6-monthly rather than annually.

As a result of the variation in reporting quality, there was a considerable amount of missing data in the data set following the initial extraction of the data from the records kept by funders. In an attempt to maximise the data available for analysis, several complementary strategies were used to augment the funder data. The first extra source of data was electronic registers of trials: reports of trials held on the Current Controlled Trials meta-register of randomised trials and the NCCHTA website were searched for additional information. Second, PIs were asked to provide information where core items were missing. Third, trial managers registered with the UK Trial Managers Network (see below) were contacted for specific information (where they were known to have had links with specific trials). Finally, the STEPS team reviewed each trial record and provided supplementary information where it was known (e.g. whether the trial team had coordinated more than one trial simultaneously).

This process of supplementary data gathering was particularly resource intensive. The authors believe, however, that the final data set is much richer as a result of this extra work and helped to provide sufficient information to allow data analysis to be undertaken. Despite all these extra efforts, however, a proportion of data items remained unclear for most trials and this is reflected in the varying numbers of trials contributing to each separate analysis.

It had been hoped that the study would identify factors associated with successful (or unsuccessful) recruitment to provide a means of predicting or enhancing the chances of success. The factors examined were chosen in advance based on previous research<sup>5</sup> and the experience of members of the research team. It is possible that other factors, such as characteristics of the trialists that were not included, might have been more informative. In the event, the comparative analyses that were performed were of limited value, both because of the choice of outcome and exposure variables, and because of imprecision around the estimates of association. While a number of these analyses provide some evidence that some factors (e.g. the intervention only being available inside the trial, having a dedicated trial manager, and

being a cancer trial or a drug trial) were associated with successful recruitment, these results (although less so for cancer trials) were also all compatible with there being no association. Furthermore, other analyses showed that some features expected to enhance recruitment were less commonly observed in 'successful' trials than in 'unsuccessful' trials. This applied in particular to 'local paid recruitment coordinators', but alternative explanations for this apparent negative association are that this comparison is confounded by other factors such as the complexity of the trial and the years when it was undertaken (see below). As many of the variables are potentially correlated, a multivariable analysis would have been desirable. There was insufficient power, however, to undertake this analysis with any degree of reliability; experts suggest that there should be at least ten observations in the data set for each potential explanatory variable to be included in the model.<sup>21</sup> A multivariable analysis was performed and the results confirmed the lack of power: coefficients were often in the 'wrong' direction and standard errors for certain coefficients were large, indicating instability in the model.

There was an apparent difference in recruitment success rates between the funders, with MRC-funded trials more likely to recruit to target. This is potentially a reflection of the different grant-awarding processes, as the HTA Programme commissions specific trials, whereas the MRC operates in response mode and this is reflected in markedly different portfolios in the two organisations.<sup>3</sup> There was also evidence that this observation may have been confounded by other factors. Cancer trials, drug trials and trials with a dedicated trial manager were all more likely to have been funded by the MRC ( $p < 0.001$  for all associations).

Two separate approaches to the analysis of recruitment success were undertaken. First, only trials that recruited to their original target were deemed to have recruited successfully. Thirty-eight trials (31%) were assessed to have recruited successfully under this definition. It was felt, however, that this definition might be overly harsh to trials that almost achieved their recruitment target, and therefore all analyses were rerun using the definition of success as having achieved at least 80% of original recruitment target. Under this definition, 68 (55%) trials were deemed to have recruited 'successfully'. Findings in respect of features associated with success (*Table 12*) were consistent under the two definitions of recruitment success.

Under either definition, however, it is clear that successful recruitment to trials is a problem. Even under the generous definition of success, only half of the trials in this study population were deemed to have recruited successfully and the situation does not seem to have improved over time (see *Figure 1*). This is despite the growing literature summarising barriers and facilitators to recruitment published in the 1990s (exemplified by the HTA review by Prescott and colleagues<sup>5</sup>). Changes in the external environment common to all trials are likely to have contributed. Some trialists undoubtedly experienced delays around the time of the introduction of the MREC system in 1997.<sup>22</sup> The climate for research was also altered by events such as the Bristol inquiry into paediatric surgery. The proportion of trials failing to achieve even 80% successful recruitment was highest in the late 1990s, contemporaneous with the height of the perceived problems with these issues. These sorts of changes could have accounted in part for the reduced recruitment success between 1997 and 1999.

The overall start to recruitment was found to have been delayed in 40% of trials. The primary reasons listed for this were associated with staffing problems. Research ethics approval delays and R&D issues did not appear to be a particularly common reason for delays given in reports to the funders, which was somewhat surprising given the weight attributed to these factors anecdotally.<sup>23</sup> While staffing issues were seen as particularly problematic for specific trials, it was apparent that a wide spectrum of problems was encountered (reflected by the high level of 'other' reasons).

As indicated above, there was evidence that cancer trials were associated with better rates of successful recruitment compared with non-cancer trials. Within the field of cancer, there has been a long-standing interest in the recruitment of patients into clinical trials.<sup>24</sup> This relatively positive and open environment for the recruitment of patients into trials culminated recently in the establishment of the National Cancer Research Network (NCRN) in England and Wales, which was created to improve the infrastructure within the NHS for clinical research in cancer and to ensure that research is better integrated with cancer care. The NCRN was established by the Department of Health in April 2001 to support prospective trials of cancer treatments and to support research undertaken by cancer charities (most of the trials included in this study had completed recruitment before this initiative was established). The aim of the NCRN is to improve the speed, quality and integration of

research, ultimately resulting in improved patient care. It hopes to increase involvement and recruitment into trials through the creation of cancer research networks across the UK closely aligned to cancer service networks. Within the NCRN all trials are conducted through accredited trials units and recruitment is coordinated through funded locally based research staff. This process of trials unit accreditation ensures that all of the core competencies (e.g. trial management, programming, statistics) are available at the coordinating centre, thus minimising the potential for trial managers to be isolated (see below), ensuring experience across the entire trial team and maximising the efficiency of the trial processes.<sup>25</sup> This approach has resulted in a doubling of the recruitment rate to cancer trials since its inception.<sup>26</sup> This approach to centralised trial coordination is currently being expanded across the newly formed UK Clinical Research Network, which aims to coordinate recruitment to clinical research (initially in six clinical areas) across the UK.

The perception that drug trials may be easier to recruit to than non-drug trials is perhaps not surprising given the background of rigour required by registration agencies and the methodological problems associated with non-drug trials. In surgery, for example, the problems with conducting randomised trials have been well documented.<sup>27</sup> With non-drug interventions, such as cognitive behaviour therapy and other operator/therapist-dependent interventions, there is the additional problem of therapist recruitment and retention over and above patient recruitment. Commentators have also indicated that trials that include innovative operator or therapist-dependent interventions suffer particularly from timing issues, where there may be only a very narrow window of time when a trial can be successfully mounted. This has been encapsulated in what has become known as Buxton's law, where "it is always too early (to evaluate an intervention), until unfortunately it's suddenly too late!"<sup>28</sup> Trials that attempt to evaluate new non-drug technologies also suffer from other problems, most notably the handling of the 'learning curve' of operators/therapists within the study, and trialists have often sought to restrict the involvement of practitioners to only those most experienced in the technique.<sup>29</sup> By restricting the number of practitioners available to be included in the trials, this has in turn restricted the eligible number of centres, and thus the patient pool available for study. New approaches to the statistical assessment of the learning curve should help to address this problem in the future.

The view that trials that had a dedicated trial manager would be associated with better rates of recruitment compared with those that did not was given some empirical support. In its recent review of clinical trials, the MRC acknowledged that the failure of some trials can be due to practical problems with trial management rather than scientific problems or problems with the trial design.<sup>4</sup> This had been recognised by the Council some years earlier and, in response to the desire to maximise the dissemination of good practice across trials, they set up a network of those people responsible for the day-to-day management of MRC-funded trials, known as the MRC Trial Managers Network. The primary functions of the network were to link trial managers together to ensure the dissemination of expertise and experience, and to establish a programme of training and support for its members. The network, which has recently expanded to include trial managers from the HTA Programme and other publicly funded trials (and renamed the UK Trial Managers Network), aims to facilitate the development of a well-trained, highly motivated, effective workforce of trial managers within the UK healthcare system who will make an important contribution to the efficient delivery of high-quality clinical trials. It also aims to establish a forum to promote best practice in clinical trials, and provide a focus for the development of skills and expertise of trial managers as part of the larger national clinical trial network. Through the promotion of this type of activity, one might hope that the standards of recruitment will increase over the coming years.

## Conclusions

Large numbers of publicly funded trials have experienced recruitment problems in recent years. Many have had extended recruitment periods, which have often been supported by additional funds. Patterns of delay were shown to vary. Many possible reasons were suggested, and a range of strategies was adopted in an attempt to improve recruitment. The simple descriptive analyses presented in this chapter do not give any clear indications of factors that are likely to predispose to successful recruitment. The explanation of why some trials consistently recruit well and others do not would appear to be complex, and not amenable to analyses of this type. Therefore, one has to look to the results of the other more in-depth components of the study for more reliable insights into the reasons for this.

## Chapter 3

# Case studies of trials that appeared to have particularly interesting lessons for recruitment

### Introduction

Many research papers start with the statement that RCTs are considered to be the gold-standard method for the assessment of the effectiveness of interventions. Trials are not, however, simply an experimental tool, independent of social, political and moral values. They are complex and dynamic entities, shaped by disparate internal and external forces. The conduct and progress of trials can, for instance, be shaped by some of their own characteristics, such as the impact of the use of placebo on recruitment,<sup>30,31</sup> the necessity for certain levels of expertise required to carry out trial interventions<sup>13</sup> and the involvement of a heavy data collection load for local centres.<sup>32,33</sup> They can also be affected by pre-existing factors such as the beliefs of the collaborating clinicians<sup>34</sup> and patient preferences.<sup>35,36</sup> Several such factors have been reported as barriers to recruitment by trialists<sup>37,38</sup> and identified in empirical studies.<sup>15,39,40</sup>

These forces create a complex microclimate in which a trial can flourish, struggle, or do both. In spite of the likely impact of this microclimate on the progress of an individual trial, research has often focused on questions raised by trials more generally, treating those with some common factors as a collective (e.g. in oncology<sup>32,41-43</sup> or in neonatology<sup>44</sup>). While this type of research is useful for mapping out broad areas of concern, the particular circumstances in which an individual trial operates, which may be crucial in promoting or inhibiting the successful working of the research, cannot be considered where trials are treated as a collective.

There is, however, a developing body of literature that uses a variety of methods, which examines the workings of individual trials and strives to understand their specific contexts. A number of single trials assesses the impact of attitudinal factors for a single trial.<sup>45-47</sup> There are several reports by trialists that describe their experience of recruitment in their own trials.<sup>48-50</sup> Gillan and colleagues<sup>23</sup> unusually describe the impact of external forces such as “national clinical, economic

and political factors” on recruitment to two multicentre trials.

These publications are pointers to a potentially fruitful area for research. It is the present authors’ contention that a careful empirical exploration of the factors that shape a number of individual trials, to consider their unique challenges and the responses of their research teams to those challenges, could afford important insights that are likely to be to the benefit of those developing other trials. It is argued that an assessment of the microclimate will promote greater understanding of the complexity of factors involved in progress in trials, and greater sensitivity to the importance of the interplay of such factors. It will also afford the opportunity to make comparisons between trials from a more informed position, to look for common ground even where the trials may be rather different. Any common factors in progress highlighted in this way are likely to be more instructive than those identified either from one trial or from an undifferentiated collective.

It is also suggested here that a search for common factors in the success of quite disparate trials that might be considered to be ‘exemplars’ (see the next page for a definition) is a positive approach that is largely missing from the available literature. Studies that have examined the performance of trials have mainly concentrated on situations where there are problems in order to understand or explain why things have gone wrong.<sup>34,49,51-53</sup> The present study therefore concentrates on trials that have, by and large, recruited well and so could be defined as successful. It is possible that a search for common factors in quite disparate exemplar trials may provide constructive data that could be used to guide and shape the development of further research.

In summary, this chapter is grounded in a drive to understand the influence of highly complicated microclimates on the success of a small number of exemplar trials and of the impact of any features that they may have in common, in spite of their

inherent dissimilarity. Unlike a number of papers in the literature, it is carried out from an independent outsider perspective.

## Aims

Part A of STEPS used reported information to give insights into features of trials and the strategies that they involved. Part B builds on this, but works with the concept that different parties who are internal to the trials will be able to offer additional role-specific and location-specific insights that are not available in these official accounts. By interviewing individuals with different internal perspectives, the possibility of producing more sensitive data is increased. Nurses, for instance, may be privy to patient reactions to the offer of trial enrolment that are unavailable to more senior doctors. Different levels of exposure may shape their views, and so their practices, within the research context. Trial managers may describe intended modes of operation, and local collaborators may explain why those procedures do or do not work well in their local circumstances. The aim is not to present a detailed analysis or a comparison of these different viewpoints. Instead, the variety of interviewee perspectives is used to produce a multivoiced, more detailed and more nuanced account of each trial.

The aims of Part B of STEPS are to use these data to describe the characteristics of individual ‘exemplar’ trials, in addition to information available from protocols, trial materials and through the reports of those closely involved with the running of the trials. Analysis of the interview data enables the exploration of the unique circumstances potentially relevant to recruitment for each trial. This element of the research aims to understand, through the opinions of the interviewees, how recruitment may be affected in a very broad sense, and so focuses on their progress, any challenges that arose and any adaptations that were made. Finally, the data were used to compare the trials in order to highlight common factors potentially relevant to recruitment.

The four Part B trials were chosen to represent a variety of clinical situations, each with its own particular challenges. As previously stated, it is precisely this variety that is of interest. Although it is not possible here to prove exactly which common factors did promote recruitment (as opposed to the perception that they did so), it is

possible to use the informed testimonies of those closely connected to the trials to generate likely factors that may be considered empirically.

## Materials and methods

### The trials

#### **Definition of ‘exemplars’**

It was intended that an examination of trials that have recruited well would produce innovative and positive data. The initial challenge for the research team was to develop and refine a definition of the type of trials that should be the subject of the study. The use of the term ‘exemplar trials’ arose during a STEPS meeting. Although an exemplar can be taken to mean something that is typical or representative (an example), it can also refer to something that is worthy of imitation (a model). It is in the latter sense that this term is employed here.

What in practice constitutes exemplar trials was not, however, immediately clear. Initially it was considered that in keeping with Part A, these trials should have recruited to their initial target. Furthermore, it was felt that they should have reached this target in the time-frame initially specified. Given the emerging findings from Part A, however, it became clear that such a rigid definition would be problematic. Therefore, trials were considered that had met or were on schedule to meet targets agreed with their funders (MRC and HTA Programme) and, most importantly, that the funders considered to be successful. If the funders of the trials categorised, and in some cases publicised, the trials as a success or as an example for other trials, then for the present purposes they could be viewed as exemplars.

#### **Access to the Part B trials**

The funders were asked to recommend a number of trials that they considered to be successful. Four trials were selected, two from each funder, and the PIs were approached to assess their interest in participation in STEPS. The PI for one trial originally selected declined because of the trial team’s plans to publish details of their recruitment strategies at some point in the future. A further trial from the same funder was chosen as a replacement.

#### **Descriptions of the trials**

For simplicity, the trials selected (FOCUS, TOuCAN, HPS and ELEVATE) are often referred to in this chapter as ‘the Part B trials’. Brief details are given in *Table 14*. The trials represent a variety



TABLE 14 Characteristics of the Part B trials

|                     |  |  |   |  |
|---------------------|--|--|---|--|
| Full title          | The Heart Protection Study   | Trial of Chemotherapy for Bowel Cancer [Fluorouracil, Oxaliplatin and Irinotecan (CPT1), Use and Sequencing] | Trial of Outcome for Child and Adolescent Anorexia Nervosa  | A pragmatic single-blind RCT and health economic evaluation of leukotriene receptor antagonists in primary care at steps two and three of the National Asthma Guidelines |
| Trial acronym       | HPS  | FOCUS  | TOUCAN  | ELEVATE  |
| Clinical speciality | Cardiovascular, health promotion   | Cancer   | Adolescent psychiatry   | Asthma management  |
| Funders             | MRC/BHF/industry   | MRC/industry   | HTA   | HTA/industry   |
| Eligible patients   | Aged 40–75 years with increased risk of coronary heart disease based on past medical history (e.g. coronary diseases, diabetes mellitus) | Advanced metastatic colorectal cancer  | Adolescents (aged 12–18 years) with anorexia nervosa referred to (but before assessment by) general and specialist providers of CAMHS                                   | Patients in primary care who have asthma which requires regular preventive treatment or an increase in therapy   |
| Eligible centres    | 69 UK hospitals  | Oncology centres meeting criteria specified in the protocol (in UK and Cyprus)                               | CAMHS in north-west England   | General practices in East Anglia and southern England  |
| Design              | Four-arm randomised trial (2 × 2 factorial)  | Five-arm randomised trial  | Three-arm randomised trial (with option to switch treatments post-randomisation, and parallel non-randomised 'naturalistic' cohort for patients refusing randomisation) | Two severity strata (steps) with two arms at each step   |

continued

TABLE 14 Characteristics of the Part B trials (cont'd)

| Trial acronym | HPS  | FOCUS  | TOUCAN  | ELEVATE  |
|---------------|--|--|---|--|
| Interventions | <p>1. Simvastatin tablet and antioxidant vitamin capsules (C, E and <math>\beta</math>-carotene)</p> <p>2. Simvastatin tablet and placebo capsules</p> <p>3. Placebo tablet and vitamin capsules</p> <p>4. Placebo tablet and placebo capsules</p> | <p>All have MdG with fluorouracil</p> <p>1. MdG, followed by irinotecan as second-line therapy (after the initial treatment had failed)</p> <p>2. MdG with oxaliplatin, as first-line therapy</p> <p>3. MdG with irinotecan, as first-line therapy</p> <p>4. MdG, followed by MdG + oxaliplatin as second-line therapy</p> <p>5. MdG, followed by MdG + irinotecan as second-line therapy</p> <p>When the trial started, cross-over to the 'other' drug (irinotecan or oxaliplatin) after completing the trial plan was discouraged, but the protocol was later amended to encourage cross-over; so surviving patients have access to all three drugs (fluorouracil, irinotecan and oxaliplatin) during the disease course</p> | <p>1. Intensive inpatient treatment</p> <p>2. General outpatient in their local service</p> <p>3. Specialist outpatient service at one of two centres, Chester or Salford</p> | <p>Step 2:</p> <p>1. LTRAs</p> <p>2. ICSs</p> <p>Step 3 (all ICS):</p> <p>1. LTRAs</p> <p>2. LABs</p>  |
| Outcomes      | Cause-specific mortality, stroke, cardiovascular events, cancer, cataract, fractures, cognitive impairment (5-year follow up)  | Survival and quality of life, toxicity, patient acceptability and health economics   | Effectiveness, cost-effectiveness and patient acceptability   | Quality of life, clinical outcomes such as asthma symptoms, hospitalisation and daily inhaled steroid dose, costs (at 2 months and over 2 years) |
| Management    | Clinical Trial Service Unit, Oxford  | MRC Clinical Trials Unit, London   | Universities of Liverpool, Manchester and York. Base is Chester Young People's Centre   | School of Medicine, University of East Anglia  |
| Sample size   |  |  |   |  |
| Original aim  | 20,000   | 2100 patients  | 210 (+70 in naturalistic cohort)  | 712 (178 in each of the 4 arms)  |
| Revised       | NA   | NA   | 165 (+75 in naturalistic cohort)  | NA   |
| Achieved      | 20,536   | 2135 patients  | 167 (+48 in naturalistic cohort)  | 356 step3; step2 ongoing   |

continued

TABLE 14 Characteristics of the Part B trials (cont'd)

| Trial acronym           | HPS                 | FOCUS  | TOUCAN                   | ELEVATE  |
|-------------------------|---------------------|--|--------------------------|--|
| Duration of recruitment | Pilot phase in 1987 |  |                          |  |
| Original aim            | 18 months           | 36 months  | 24 months                | 7 months   |
| Actual                  | 36 months           | 42 months  | 42 months                |  |
| Period of recruitment   | 1994–1997           | May 2000–December 2003   | April 2000–December 2003 | 18 months step 3; step 2 ongoing   |
| Extension               |                     | No extension required; extra 6 months of recruitment absorbed into 5-year time-frame for the trial |                          | May 2002–November 2003 (step 3); May 2002 to at least December 2004 (step 2) |
| Time only (no cost)     | Yes                 |  | Yes                      | Extension of time and costs (and reduced length of follow-up for step 2)     |
| Time and costs          |                     |  |                          |  |

BHF, British Heart Foundation; CAMHS, Child and Adolescent Mental Health Services; ICS, inhaled corticosteroid; LAB, long-acting beta-agonist; LTRA, leukotriene receptor antagonist; MdG, modified de Gramont; NA, not applicable.

of settings, methods and clinical specialities. Two are hospital based (FOCUS and HPS), one involved a comparison of inpatients and outpatient services (TOuCAN) and another assessed primary care (ELEVATE). None of the trials is a simple two-arm parallel group trial; they range from a five-armed trial with cross-over (FOCUS), to a three-armed patient preference trial (TOuCAN), a stratified trial (ELEVATE) and a factorial trial (HPS). The clinical specialities involved are cardiovascular health promotion (HPS), oncology (FOCUS), adolescent psychiatry for anorexia nervosa (TOuCAN) and asthma care (ELEVATE). All of the trials are multicentre. In three of the four trials there are drug interventions. One trial (HPS) involves the use of placebo. The possible outcomes of the trial interventions reflect the different settings and patient populations involved, with two of the trials involving assessment of mortality (HPS and FOCUS). In two cases (HPS and FOCUS), the trials are managed by large clinical trials units, in one by an academic unit (ELEVATE) and in another, management is shared by two branches of a regional service (TOuCAN). The absolute sample sizes for the trials may be less relevant than the fact that in each case the trials were intended to be the largest in the world for their population. All of the trials involved an extended period of recruitment, of which one required a time-only extension (HPS) and two required additional funding (ELEVATE and TOuCAN). Target sample sizes were revised for the TOuCAN Study. Recruitment is complete and the planned numbers are exceeded for two trials (HPS and FOCUS), and recruitment is ongoing for the other two with targets likely to be achieved.

### **Access to interviewees**

#### **RECs and trust R&D requirements**

At the time of the original application to fund STEPS, REC approval for interviews with NHS staff was not normally required. However, new regulations were instituted and it became necessary to submit a full REC application for this component of the research. As MREC approval under 'no local researcher guidelines' was given, there was no need for applications to LRECs, but the new research governance guidance, also instituted since the start of STEPS, caused further delays. The study was not viewed uniformly by the R&D staff. The researcher consulted with 12 R&D offices and was advised to make applications in each instance to conform to local requirements. While some centres had rigorous requirements, including applications for honorary contracts, provision of references, completion of

occupational health forms and a police check (requested, but later waived after some discussion on receipt of the study paperwork), three R&D offices revised their opinion that an application was necessary. The formal process of negotiating ethical and R&D approval took a disproportionate amount of researcher time for this short study, and has negative implications for conducting such research in future.

#### **Recruitment of interviewees**

Before the start of interviews, a broad model of the likely candidates for interview was drawn up, reflecting the researchers' concept of the relevant protagonists in the running of clinical trials. It was considered important to include those with a range of roles, not to characterise the views of different professional groups, but on the assumption that those with different responsibilities and experiences will have different insights into the four trials. There is little research that assesses the views of such various contributors. Although there are some reports of the views of nurses<sup>54,55</sup> and some of the views of GP recruiters,<sup>37,56-58</sup> the research samples available are largely comprised of senior doctors involved in trials, with a strong bias towards oncology trials.<sup>32,41-43,45,59,60-62</sup> No research was identified that describes the attitudes of coordinating staff [although see Rico-Villademoros and colleagues<sup>63</sup> for a survey-based description of the role of the clinical research coordinator (data manager) in oncology trials].

The original aim was to carry out 32 interviews, eight per trial, with a split between the central coordinating staff and the staff from the recruiting centres. The sample was constructed to represent key players who could describe the workings of each of the trials. The intended interviewees were PIs, trial managers, local lead consultants and local recruiters (doctors or nurses according to the trial procedures). As understanding of the processes involved in each trial increased, the list of likely interviewees was expanded to fit the unique circumstances of that trial. For the ELEVATE trial it became clear that there were both research assistants and agency-employed research nurses with key roles in recruitment who could not be omitted from the study. For two of the trials there were two joint PIs. For the TOuCAN study there was no research nurse involvement in the trial and recruitment was carried out by non-clinical trial staff who had not been included in the original list of interviewees. Ultimately there were 45 interviews in total (*Table 15*).

**TABLE 15** Sample structure for Part B

|   | FOCUS | ELEVATE | TOuCAN | HPS | Totals |
|---|-------|---------|--------|-----|--------|
| Central coordinating staff  |       |         |        |     |        |
| PIs   | ✓     | ✓✓      | ✓✓     | ✓   |        |
| Trial managers  | ✓     | ✓       | ✓      | ✓✓  |        |
| Central recruiters  |       | ✓✓      | ✓✓     |     |        |
| Administrative support  |       | ✓       |        |     |        |
| Statistician  | ✓     |         |        |     |        |
| Clinical support  | ✓     |         | ✓✓     | ✓   |        |
|   | 4     | 6       | 7      | 4   | 21     |
| Clinical staff in recruiting/referring centres  |       |         |        |     |        |
| Local lead investigators  | ✓✓    | ✓✓✓     | ✓✓✓✓✓  | ✓✓  |        |
| Recruiting doctors  | ✓✓    |         |        |     |        |
| Recruiting nurses   | ✓✓✓   | ✓✓✓     |        | ✓✓✓ |        |
|   | 7     | 6       | 6      | 5   | 24     |
| Total staff   | 11    | 12      | 13     | 9   | 45     |
| Key to shading: <span style="background-color: #cccccc;">■</span> , recruiting staff; <span style="background-color: #e0e0e0;">■</span> , central coordinating staff; <span style="background-color: #f0f0f0;">□</span> , clinical staff in recruiting/referring centres. |       |         |        |     |        |

The respondents were recruited from the four trials with a combination of purposive selection methods, and elements of snowball sampling. Access to the PIs was facilitated by the funders. The PIs in turn facilitated access to the central trial team. For the local centres, letters (Appendix 4) including information sheets describing the research (Appendix 5) and consent forms (Appendix 6) were sent out directly by the trial teams either by e-mail or by post to the trial mailing lists. Those interested in taking part in the research were invited to respond by replying to the researcher rather than to the trial team, thus maintaining a degree of confidentiality for those respondents in relation to the central trial team. Where more people responded than were needed, interviewees were selected randomly. On some occasions, individuals advised the researcher that it would be appropriate to speak to a colleague. In these instances the informant was asked either to make contact on behalf of the study, or to check with their colleague that they were happy for the researcher to make direct contact. In a small number of cases the researcher made an unmediated direct approach to individuals who were detailed in the trials literature who seemed to be potentially important to the study. It is not possible to give a response rate as it is not known how many individuals were contacted initially.

Table 15 shows the broad division of interviews between central coordinating staff ( $N = 21$ ) and

clinical staff in recruiting or referring centres ( $N = 24$ ). These two categories do not, however, reflect a simple split between recruiters and non-recruiters. Recruitment was not carried out exclusively by the staff in the recruiting centres, and within the recruiting centres not all staff had a role in recruitment. In the FOCUS trial the PI had a clinical caseload from which trial participants can be recruited, and for ELEVATE and TOuCAN there were members of the central office team who had specific duties to recruit to the trial. In the recruiting centres there were some staff whose role was to facilitate rather than to carry out recruitment. The distribution of recruiters ( $N = 16$ ) and non-recruiters ( $N = 29$ ) is also indicated in Table 15, with recruiters marked with the heaviest highlighting.

#### Interview structure

All interviews were carried out by telephone in the period from December 2003 to May 2004. They were tape-recorded with the consent of the interviewees and fully transcribed. The discussions typically took between 20 and 80 minutes, depending on respondents' degree of involvement in a trial. The interviews were semi-structured and explored respondents' opinions about the Part B trial in which they were involved (Appendices 7 and 8). The interviews did not include discussion of individual patients. They were wide ranging, highlighting individual responsibilities and their attitudes to and experiences of the trials.

Interviewees were also asked to rate the importance of the question addressed by their trial and the quality of the design on a 0–5 Likert scale.

The very detailed discussions were not only designed to promote a full and reflective account of their involvement, but also aimed to promote in the interviewees a deeper state of engagement with the issues raised. When, at the end of the interviews, respondents were asked to identify key factors in the success of their trial, and if there were any issues that were important and had not been discussed, the researchers were confident that their accounts and their final summaries were well considered and reliable. Because the study involved professionals with a variety of roles within the trials, the questions were to some extent varied for each of these individuals. The lines of questioning were also modified and developed over the period of the fieldwork, in response to the insights gained.

### **Analysis**

All of the interviews were conducted, read and analysed by one of the researchers for Part B (CS), with research colleagues (JG and DE) reading a sample of the interview transcripts and commenting on significant portions of data as requested. Data analysis was conducted with the assistance of the qualitative package Atlas-ti. The analysis was shaped by the research aims to provide descriptive, exploratory and comparative data.

To some extent, the data are a product of the questions that were asked and could be said to be influenced by the research team's pre-existing perception of what was likely to be important rather than pure themes that arose from the data. However, many issues arose in response to the direction of the interviewees, and the organisation and refinement of the data are very much a result of the analysis. In his 'adaptive theory', Layder<sup>64</sup> values the role of pre-existing researcher knowledge and concepts, in comparison to grounded theory approaches in which the data collected are primary and from which themes are said to emerge. He suggests an approach to analysis in which existing models are adapted in a process of modification and refinement as experience and understanding of a phenomenon grow. In this way, for Part B, an initial line of questioning was drawn up for the interview schedule; it was developed in interview as interesting lines of information were introduced by respondents, and then explored in analysis. Analysis commenced with codes based on a

mixture of the interview schedule and insights gained from the interviewer's experience of the interviews. The codes were expanded and collapsed as each interview was processed. Eventually no new codes were introduced and the researcher was satisfied that the data had been adequately explored.

The findings from the descriptive, exploratory and comparative data are presented in three parts. They are first organised as four case studies in which the structure, history and progress of each trial is described. The data are then presented as key chronological stages in the development and conduct of the trials, ordered thematically within and across the four trials. Finally, possible common factors in recruitment success, as suggested by the interviewees, and generated by the data analysis, are presented.

Where appropriate, quotations are attributed to particular trials and 'type' of respondent. However, in some instances, no attribution is given, to protect anonymity.

## **Results**

### **Brief histories of individual 'exemplar' trials**

#### ***The FOCUS trial***

The FOCUS trial was developed to address the issue of how best to treat patients with advanced metastatic colorectal cancer, in the light of the development of two drugs, irinotecan and oxaliplatin. These drugs were evaluated in previous trials but had not been directly compared, nor had there been direct comparison of the same drug used in first- or second-line therapy.

The developmental period for this trial was lengthy, in part because of a process of clinical and academic consultation with colleagues and professional bodies. Negotiations with industry for access to, and funding for, the study drugs were protracted and added to the delays in set-up. A potential consequence of such delays was a shift in the evidence base, which would disrupt the trial at a later stage.

In 2002 the National Institute for Health and Clinical Excellence (NICE) argued that existing and emerging data on the improvements in survival times for the drugs used in the FOCUS trial did not warrant the costs involved with their routine use in first-line therapy, and issued

guidelines which largely limited off-protocol access to the drugs.<sup>65</sup> NICE recommended that irinotecan should be used, but only after the failure of a first-line treatment, and that the use of oxaliplatin be restricted to a small subcategory of patients. There were two consequences of the guidelines. First, except for that subgroup, oxaliplatin was now available only via the trial, to which NICE recommended recruitment. Second, NICE had recommended the use of second-line irinotecan when first-line treatments had failed, when two of the arms in the trial did not employ irinotecan. The NICE guidance caused a furore in the oncology community, with some oncologists arguing in a letter to a newspaper<sup>66</sup> that NICE had misinterpreted the available data.

After another period of consultation with the professionals involved in the trial, the trial team adapted by amending the protocol to remove the existing discouragement to post-trial cross-over and introducing a balanced cross-over policy. All surviving trial patients would then have equal access to either oxaliplatin or irinotecan depending on the trial arm, after completing their initial trial treatment. In response to public debate following NICE guidance, the independent trial steering committee (TSC) took the unusual step of publishing a letter defending the trial management group's decision to continue accrual.

The letter<sup>67</sup> included a statement that the data monitoring and ethics committee (DMEC) had reported no safety or ethical reasons to close the trial, and also included current overall median survival data for the trial as a whole. The aim was to assuage concerns that patients were being deprived of the opportunity of improved survival. The recruitment rate remained steady in this period.

The trial exceeded its aim to recruit approximately 2100 patients, accruing 2135 patients, but over 3.5 years rather than the planned 3-year period.

#### **The ELEVATE trial**

The ELEVATE trial was developed in response to a call for applications by the HTA Programme. It compares the role and cost of a relatively new class of orally administered drugs, LTRAs, to ICS and LABs (see *Table 14*) for primary care patients who have asthma that requires regular preventive treatment or an increase in therapy. LTRAs have been available for around 7 years and can be prescribed for asthma patients, but more often LABs are used. Although LTRAs are more

expensive than conventional drugs, they are in tablet form and may prove to be more acceptable than inhalers, so promoting better disease control.

The ELEVATE trial is framed by the five 'steps' of the British Thoracic Society National Asthma Guidelines. Eligible patients are those judged either to have progressed in their condition or to have poor control of their symptoms and so need an increase in their medication: they need to be 'stepped up'. As the trial is pragmatic, aiming to produce 'real-life data', it includes patients who would be traditionally excluded from asthma trials, such as smokers or those affected by other conditions.

The trial was very much shaped by its location in general practice. Trials in this area are known to be difficult.<sup>47,58,68</sup> There was, however, an important advantage for the trial in that GP contracts require that a high proportion of patients with asthma are regularly reviewed, and that poor control of asthma is addressed. Participation in the ELEVATE trial offered practices a valuable degree of support with this potentially onerous task.

Recruitment was initially very slow. The trial team had expected to provide some administrative support to the practices, but it became clear that much greater involvement in the recruitment process was required. The entire approach to recruitment was revised. Funds were granted by the HTA Programme to provide a more intensive level of assistance and additional staff costs, and to permit an extension to the recruitment period. Money from a pharmaceutical company supported baseline practice audits and excess drug costs. At the time of this research (July 2004), recruitment to one stratum is complete and is ongoing for the remaining stratum. A reduction in the length of follow-up for this stratum has enabled the recruitment period to be further extended without an additional extension of the amount or period of the funding.

#### **The TOuCAN study**

For some time the senior researchers for the TOuCAN study had wished to carry out a trial assessing the efficacy of approaches to care for adolescents with anorexia nervosa. They were keen to understand whether it was better to have intensive inpatient treatment at an earlier stage in the condition, or whether this should be reserved for the more difficult, entrenched cases. They also wished to assess the possible value of a recently developed specialist outpatient service. RCTs are

not widely used for this condition and previous attempts to bring about a trial had been unsuccessful. There were many practical and attitudinal obstacles to be overcome to set up the TOuCAN study. In a setting where there are deeply held lay and professional beliefs about approaches to treatment, the researchers had to work hard to meet colleagues' concerns and to promote support for the development of a trial.

Once funds were awarded there were several practical and attitudinal obstacles to be addressed. These were a highly complicated mix of local concerns over responsibilities for patients, about delivery of care and about the impact of the trial upon professional standards and autonomy. Despite this rather difficult climate, the trial did gain the support needed. In addition to the efforts made by the central team to maintain the profile of the trial and to gain access to potential participants, an important element in securing professional support seems to have been the opportunity for hard-pressed clinicians to access expert assistance with an often intractable, time-consuming and anxiety-provoking condition. Some clinicians were uncomfortable with passing over control of their patients in the trial context, but others welcomed the opportunity to free up local time and resources.

It became clear that although a very impressive 90% of cases were entered into either the trial arms or the naturalistic arm, the recruitment targets of 210 in the RCT and 70 in the naturalistic arm were not going to be met. With new power calculations the targets were revised to 165 and 75, respectively, and a funded extension was awarded. These targets were reached in 3.5 years instead of 2 years.

### **The MRC/BHF Heart Protection Study**

The HPS was based at the Clinical Trial Service Unit (CTSU) in Oxford. It aimed to evaluate cholesterol-lowering therapy (statins) and antioxidant vitamins for a diverse group of patients at increased risk of coronary heart disease (previous coronary disease, other occlusive arterial disease, diabetes, hypertension). The trial grew out of a pilot study which was funded by industrial sponsors and started recruitment in 1987. As a result of this work the trial team concluded that a much larger and more ambitious trial was needed than had been previously anticipated. There were questions about the role and safety of statins, in particular whether they would reduce mortality and morbidity even in those with cholesterol levels that were below average for the UK population. In

addition it was considered important to explore the impact of dietary supplementation with antioxidant vitamins. At that time they were thought to have a potential role in protecting the body from the adverse effects of high cholesterol.

With the initial sponsors unwilling to fund such a trial, it was necessary to bring together a consortium of funders. The trial eventually cost £21 million and was funded by the MRC, the British Heart Foundation (BHF) and two pharmaceutical companies who manufactured the statins and the vitamins. Securing this degree of funding, while maintaining academic independence and control of the research questions, was hugely difficult and time consuming, and the main trial suffered major delays as a consequence, finally starting recruitment in 1994. The delay may have led to a dilution in the difference in cholesterol levels between the statin arm and non-statin arms as clinicians increasingly prescribed statins as results from other studies became available during the course of the HPS.

The trial was randomised and double-blind, and used a 2 × 2 factorial design; around 5000 people were allocated to each of four treatments: (1) active statin and active vitamins, (2) active statin and placebo vitamins, (3) placebo statin and active vitamins, and (4) placebo statin and placebo vitamins.

The trial was thought to be well timed in terms of clinical awareness of the need for an answer to important questions about management of cholesterol, but the feature that shaped the progress of this trial was its size. Many management issues were focused on how best to control and direct human and other resources. For instance, 69 UK hospitals participated in the trial. In all, 131,000 invitations were issued and 63,603 people between the ages of 40 and 80 years were screened. Of these 32,145 agreed to enter the 2-month run-in to the study and 20,536 finally took part (15,454 men and 5082 women). Loss to follow-up was less than 1%. Identification of potential participants was carried out by the central trial coordinating team and this was recognised as critical to the success of the study; local consultants and research nurses would simply not have had the time to do this. It also allowed the central trial team to target categories of patients whose participation they wanted to increase, such as women and older patients. Study clinics in the hospitals were run by specially recruited senior nurses and participants attended



these clinics regularly over their 5-year period in the trial. The nurses were trained centrally and given considerable autonomy.

The trial succeeded in its aim to recruit around 20,000 patients between the ages of 40 and 80 years over the period 1994–1997 and has reported its results.<sup>69–71</sup> HPS gives STEPS an example of a successful, large, ‘simple’ or ‘streamlined’ clinical trial with important, internationally significant results.

### Exploration of the key stages of the trials processes

As these descriptions of the trials suggest, there is a number of phases in the course of trials, each involving different challenges that the trial teams have had to address. It would seem that it is important to consider how these different stages contribute to the level of recruitment to a trial. Four key stages of the trials that may affect recruitment were identified through the analysis. They are:

- key stage 1: Foundation work (engagement of collaborators; establishing scientific rigour; funding and financial considerations)
- key stage 2: Recruitment processes
- key stage 3: Delivery of care
- key stage 4: Delivery of research.

These stages are analytical constructs, rather than chronological stages, and involve a certain degree of overlap.

#### **Key stage 1: Foundation work: engagement of collaborators**

Trials take place in clinical settings in which the professionals involved are autonomous or can act within a firmly integrated community. Within the broader clinical communities, a research community can be more, or less, well developed at the start of a trial. Even where research is carried out, it may or may not involve RCTs. The interviews with the PIs and some of the staff who had been associated with the early stages of the Part B trials involved discussion of the preparatory or foundation work that they carried out to enthuse and engage their community in their research, and to maximise the support of potential collaborators.

The professionals on whom they depended had varying degrees of research experience and enthusiasm for the trials. For the TOuCAN study (anorexia nervosa) and the ELEVATE trial

(asthma), there were limited pre-existing clinical networks in which some individuals had been associated with earlier research collaborations, but there was work to be done in bringing the wider community together as a collective with a committed research identity. The HPS cardiovascular and the FOCUS trial (colorectal cancer) were, by contrast, conducted in the context of rolling programmes of trials, where professionals were familiar with trial rationale and procedures and in which there were established networks of research collaboration. Some of the “work behind the scenes” (TOuCAN study interviewee) described in the interviews was to establish the clinical and scientific basis of the trials and was carried out before funds were awarded, and some took place in the early postfunding stage. Typically, it involved senior professionals in the field. How the trials were received appeared to be very much a product of the degree of research experience held by these communities.

The TOuCAN study drew on the support of what was described as the “small world” of adolescent psychiatry in the north-west of England and was carried out by a newly developed research team. From the start there was a number of major obstacles to overcome in order to bring about this “difficult”, “mammoth trial”, but one of the interviewees described how they felt that it offered an important chance to develop the research experience and profile of their community:

Adult mental health services hadn’t been very successful in treatment trials in this area and here was an opportunity for child psychiatry, [which is] a bit of a Cinderella speciality, to come up with some good research.

Although there are academic units in the area, and some interviewees who were linked to these described themselves as “pro-research” and “very research orientated”, the image generated by the TOuCAN study interviewees was a community that was not naturally drawn to RCT methods. RCTs are seldom used in connection with anorexia nervosa and so there was not widespread experience with trials. One interviewee stated that “up here it’s unusual for people to be in treatment trials” and another felt that the trial focus on the care of children and adolescents further complicated things:

Child psychiatry is a very young branch [so there is not as much research] as you have in other branches of medicine. There are [also] some people who don’t believe in quantitative research. In psychiatry there is much more [support] for qualitative research.

There were, however, concerns about the TOuCAN study that went beyond research methods and these constituted a major challenge to establishing the trial. There were concerns about limitations on professional autonomy and erosion of skills in a system where cases of anorexia nervosa are randomised away from local care. Although the primary aim was to delineate appropriate services, the way in which inpatient and outpatient care was used within the trial caused much professional anxiety. Inpatient care involves removal of anorexic adolescents from home, school and family to a difficult environment and exposure to a range of highly problematic psychiatric conditions. Although this approach is traditionally reserved for urgent cases, it can still be difficult to find inpatient beds. Randomisation meant that patients in far less extreme circumstances may be allocated to inpatient care, and that some in a more advanced condition be allocated to outpatient care. Although the trial was premised on uncertainty over the value of these different approaches, some clinicians found it difficult to countenance this situation. Some concern was expressed in interviews that if urgent inpatient care was requested, beds could be blocked by “more robust” trial patients.

These concerns highlight a major difficulty faced by the trial team. To answer the research questions necessitated recruiting the vast majority of cases of adolescent anorexia nervosa in the area. To achieve this ambitious aim it was crucial that this clinical community, in which there was a significant degree of ambiguity over the proposed research, should work collectively and efficiently towards that end. Although the interviews indicated that there are some enduring areas of unease, the trial has in fact been well supported. This may have been due in part to the efforts made by the trial team to address any community concerns through meetings and provision of information, and it seems that some concerns may also have been offset by the very localised setting for the research. Although the PI had not previously conducted a trial himself, he had worked in a number of key centres in the area, had established treatment programmes and had worked with many of the local senior adolescent psychiatrists. Along with other senior clinicians involved in the TOuCAN study, he was aware of local politics and sensitivities and was familiar with his colleagues’ concerns about a trial for this condition. Most importantly, he had a clinical load and often took referrals of difficult cases from CAMHS colleagues in the area. He argued that this active clinical position was crucial in terms of

engendering trust and professional relationships. He felt that a trial in such a setting would be doomed to fail without the support of pre-existing clinical networks:

It would be difficult for an academic to propose this sort of trial without having the clinical standing. We here are very embedded in the [local] clinical service, and so I think if an academic proposed the research and just hoped to get clinicians on board, they wouldn’t be successful. I think you have to have referrers’ confidence that patients are going to be managed by somebody with expertise in the field.

The interviews with the local CAMHS professionals involved in the TOuCAN study amply supported this statement. Despite some difficulties, the interviewees were keen to contribute to research in their area, and to support a colleague whom they either knew personally or admired professionally. He was said to have “a name” in the field and interviewees said that they were “impressed with what [he] was trying to do”, and that “a lot of people would want to try and support the trial partly because of [the PI] being the one who’s leading the trial”. One of the CAMHS professionals said: “I felt favourable towards the trial at the beginning because I know [the PI] and like him and because he had helped me to think about how to manage anorexics.”

Similarly, the GPs interviewed in connection with the ELEVATE trial of asthma therapy were aware of the work and profile of the PI and welcomed the fact that he was himself a GP. His name was said to carry “a huge amount [of weight]” by one of the GPs. This was particularly important in this setting as general practice is a hard-pressed area of medicine in which trials can be difficult for practical, methodological and ethical reasons.<sup>68</sup> The ELEVATE trial was no exception to this and GPs who were interviewed talked about the need for assurance that the research would not adversely affect their workload, their finances and their patients. The active presence of a GP as the PI, and a process of consultation with a small GP research consortium carried out to guide the development of the trial, had promoted an influential sense that the trial had emerged from within primary care and so would be sensitive to its particular priorities and limitations. The interviewees who were members of the consortium felt that they were part of a research network and felt a degree of loyalty to the trial, even though it was not considered to be the easiest of research areas:

[We were] very much involved in the design of it at the beginning so we had a lot of ownership of the

project and obviously we were going to be happy to go ahead and recruit for it and very actively support it. ... Had it been [anyone else as PI] I think we wouldn't have done it because we felt our asthma patients had already been approached three or four times in the last four years. But [we did] because we'd been involved in this and we'd thought things through and it's made as easy as possible for the practice.

Although the ELEVATE trial drew some advantages from the GP research consortium, it still proved to be quite a task to pull together a sufficiently large group of practices to conduct the trial. One GP explained some of the possible reasons why research that requires active GP input can be problematic:

There is a very strong feeling among grass root GPs that they don't see why they should do it themselves, in their time and why they should be [subsidising] it. ... [It has to involve] questions that the GPs are interested in and that are relevant to general practice and often research projects come up with questions that actually seem particularly irrelevant. There's a slight suspicion of academia and research in general practice. A lot of people feel that you should be out there on the front line seeing the patients and are very sceptical about research in general.

The trial team ultimately had to extend the geographical area for the trials, and to contact over 300 practices to find the 55 that went on to become recruiting centres.

By contrast, the remaining two trials were located within nationally based networks of experienced and convinced research collaborators. The HPS followed on from earlier trials and from a funded pilot study. One of the consultants interviewed argued that his previous experience with the standard of administration and the quality of trials run by the CTSU was highly influential in his decision to collaborate with HPS. Collaborators from the pilot study were available to the main study and additional centres were brought on board through a process of visiting new centres and building up networks. The set-up period for the 69 centres that went on to collaborate with the trial proved to be "more time consuming" than had been anticipated. For the earlier collaborating centres there was thought to be a pre-existing "trial ethos", but in some of the new centres there were actually very few trials taking place.

For this trial a range of professional groups was targeted as potential collaborators. Interest in the research was a more important factor than speciality and so collaborators included, for instance, neurologists, diabetologists and

biochemists, as well as cardiologists. The trial team were very much aware of the need to promote a strong sense of enthusiasm for the trial among their recruiting centres as their contact had to take on a role as a local representative of the trial, and the recruiting centres were required to act rather independently from the central office (see below for more details of recruitment):

[It] was very important to establish that connection because with HPS, unlike some of the other trials we do, ... where we were getting data from the hospitals, there were patients under consultants ... other than the doctor that we had as our contact. ... Having them on side was critical.

A balance had to be struck, however, as the trial team were not in the "luxurious position" of selecting only the most committed centres, but they did feel that a "friendly relationship was critical".

A possible obstacle to the engagement of collaborators for HPS was the anxiety among some potential collaborators that lowering cholesterol, the primary aim of the trial, was potentially hazardous. It was therefore important that such areas of concern could be addressed at an early stage. This was done through meetings in which the team presented the evidence and rationale for the trial, and through setting up a telephone information help-line for any queries that collaborators might have.

The advantages of being able to draw on a substantial existing research community were particularly evident in accounts of the developmental period for the FOCUS trial, a trial with a very different starting point from those just described. The trial was run by the MRC Clinical Trials Unit and was introduced into the cancer research community, which has a well-developed infrastructure and a shared history of successful and committed collaboration within oncology. Where a sense of academic loyalty and shared research experience already exists, this was considered to be an important advantage, as described by one of the central team members:

[It] very much built on what we've done in the past. One of the advantages of having a trials office like us who run a series of trials in a certain disease, is that we build up contacts and we build up rapport with the clinicians. So we had a very successful trial [previously] in the same group of patients and it was all the same clinicians basically. So having built that kind of community, when we started to promote the idea of having the next trial for the same group of

patients, we had all the mailing lists for that group of clinicians, and they were the same group of clinicians who turned up at all the meetings etc etc. So that was a very good foundation for starting off. We were starting from quite a high level of interest.

There was very much a sense that the development of the FOCUS trial was fostered by an experienced and professional community. The set-up period for this trial involved a process of consultation with many senior clinicians and professional bodies. The aim was not only to produce a trial of sound design, which would reflect the concerns and interest of many of the senior figures in the field, but also to promote a sense of commitment to recruitment among potential collaborators. This resulted in a trial that was described very positively and characterised by collaborators in interview as “democratic” and “very smooth”.

For the FOCUS trial there was a sense of enthusiasm and opportunity that was clear in the interviews. Trial participation was largely seen as important for developing strategies of care for future patients, but also as offering potentially important options for existing patients, especially in terms of the chance to access “cutting-edge” drugs. It was seen as a “win-win situation”. A number of interviewees described the enthusiasm of this research community and a sense of excitement felt at the launch meetings for the trial. The collaborators were said to be very keen to start to use the study drugs and to be involved in a trial that was “groundbreaking”. The enthusiasm has largely continued through the trial. It appeared both to promote and to maintain levels of support for the trial, possibly a major factor in successful recruitment, which was commented upon by one of the trial coordinating team:

[For] trials that don't recruit so well, [it must be] difficult to try and drum up attention when it's falling on deaf ears. Whereas it's ever increasing circles when people are responsive and you're enthusiastic. It just builds momentum.

### **Key stage I: Foundation work: establishing scientific rigour**

Part of the process of promoting and engaging collaborators is to gain their confidence and intellectual support. The research focus and the methods used are defining elements of a trial. It was clearly of value to the trial teams interviewed here to feel that their research was asking an important question in a methodologically sound way. The importance was not only for the team

and funder's confidence in the trial: perceptions of the quality of research have been shown to have directly affected clinicians' willingness to recruit their patients.<sup>51,72</sup> A crucial part of the foundation work for the trials was therefore to establish the scientific credentials of the trial. The interviews for STEPS included discussion of the importance of the research question and the level of scientific rigour of the trials.

### **Importance of the research question**

It was striking that when the interviewees were asked for their views on the importance of the research question, they frequently responded in terms of its clinical rather than academic relevance. It was obviously important to the interviewees that the trials should be practical and applicable and the hope behind a comment made in connection with the FOCUS trial was echoed throughout the interviews across the trials: “It could change the course of the treatment of GI [gastrointestinal] cancers.” For the ELEVATE trial an important factor in terms of the applicability of the trial results was the common nature of the disorder. A research assistant commented on this: “it's very important because lots and lots and lots of people have asthma ... so I think the question's very relevant, and very real.” Similarly, there was considerable enthusiasm among the interviewees for HPS, because of the relevance of the research to a large clinical population. A nurse who described the question addressed by HPS as “exceptionally important” explained:

It's such a high risk to the population, all of these conditions, and especially the cardiovascular conditions, that if we could find a way of reducing the risk to people, then you know we could certainly reduce the mortality and incidence within Britain, because it has been gradually increasing.

In contrast, the TOuCAN study focused on a quite rare condition, for which the available approaches to care are not currently evidence based. Its value lay not in a broad application but as an empirical starting point. One interviewee commented that the question was “a very crucial [one] because no-one knows and there are no trials”. Similarly, another said: “there's a big hole in the literature in regard ... to the treatment of anorexia nervosa in adolescents ... so it is going to be highly useful.”

For all of the trials there was also appreciation of and interest in the more challenging aspects of the research questions, such as accessing populations that are under-represented in research (TOuCAN, ELEVATE and HPS) and assessing interventions

that could arouse a degree of clinical controversy (FOCUS, HPS). The trials were often seen as “ambitious”, “difficult” and “cutting edge”.

While the PIs and their supporting team were not surprisingly enthusiastic and very clear about the value of their research questions, they were aware that support for their research could not be taken for granted. In each trial the trialists knew that in the initial stages some colleagues were not convinced of the need for information, or were happy with their existing approaches to care, and they had to work to address this problem. For HPS there was “quite a lot of resistance in the medical world”, which this interviewee said had been “overcome enormously”. Similarly, where there was support for the FOCUS trial it was said to be “clear and unequivocal”, although the trial also had its objectors. For the ELEVATE trial there was discomfort among some GPs as they were being asked to consider working outside the approved national strategies for asthma care. The teams therefore put a great deal of effort into promoting understanding for the need for research evidence in their specific areas. The PI for the TOuCAN study had a policy of telephoning colleagues who had queries, to address personally any concerns that they might have about the research. The four trial teams also hosted or attended clinical meetings, ran training days and made visits to recruiting centres. The interviewees who had attended trial events were very enthusiastic about both the educational and the social aspects. HPS offered residential study days and these appeared to be particularly popular.

Even though the Part B trials involved quite different types of research questions, the interviewees seemed to be equally enthusiastic about the value of the research question. Each of the trial questions was regularly described as being “important”, “good” and “interesting”. The importance of the question addressed by their trial was rated by interviewees on a 0–5 Likert scale. All gave a rating of 4 or 5. One interviewee commented on the value and influence of a well-considered research question for their trial:

It seemed to be the question that people wanted answering. It's quite interesting that if you get the question right, everything else seems to sort of be so much more smooth.

### **Design of the trial**

All four Part B trials were viewed very favourably by the interviewees in terms of their methodological quality. When the interviewees

described the importance of the research question it was frequently and spontaneously expressed in connection with their confidence in the design of the trial to deliver results; essentially they felt that the trials were scientifically robust. As with the importance of the question addressed by the trial, the quality of the design was rated by interviewees on a 0–5 Likert scale. Almost all interviewees gave a rating of 4 or 5.

For some of the interviewees, such as the PIs and other senior trialists, this response was from a more informed perspective, not only because they knew the trial intimately, but also because they were familiar with factors such as power calculations and the implications of elements of design such as permitting cross-over. For some other interviewees, it related in part to their faith in the prime movers for the trials. One local clinician talked about his admiration for the “fantastic work” done by the PI in producing a “brilliant trial protocol”. For another trial it was perceptions of the acuity involved in pitching and delivering the trial: “Their knowledge about how to decide which questions to answer is probably second to none.”

There was a sense for all of the trials of striving to maintain the quality of the design in the face of quite onerous challenges. For the TOuCAN study the referring consultants appeared to appreciate the difficulties inherent in this trial, and perhaps this added to their wish to see the research succeed. When asked to reflect on the design of the trial, one consultant commented:

I was involved in another study which wanted to compare inpatient with outpatient treatment and they never got it off the ground. You know, it just didn't deal with the realities of life. [The TOuCAN study] has dealt with the realities of life. In view of the difficulty of the task and the importance of work like this, it seems to me to be pretty damned good.

The PI was clear that this trial only worked in such a difficult clinical setting because he was prepared to tolerate a degree of compromise in the design. He was the only interviewee in the study to give the quality of the design of their trial a rating of 3. He was clear, however, that any compromise to the design was born out of realism in order to make the aims of the research achievable:

It's a compromise in terms of the treatments being evaluated and it's a compromise in order to maximise the chances that the patients will consent to take part. ... I think it was the best compromise to persuade clinical colleagues to take part.

### **Key stage I: Foundation work: funding and other financial considerations**

How financial costs are met and distributed is possibly one of the most crucial factors in the success of a trial. Securing the initial funds is a challenge in itself. Once these have been granted there are additional areas in which financial issues can play a part in shaping the research. If the initial funds are limited, or there are unanticipated increased costs, there is the inherent difficulty for the trial team of running a trial with inadequate funds to consider. There is also the likelihood that financial considerations will affect potential collaborators' decisions about their involvement. Potential costs or savings are likely to be factors in their decisions about whether or not to collaborate in a trial at all, and also how much effort to put into that collaboration.

Of the four trials studied here, the TOuCAN study was the only one where it was widely perceived that recruitment to the trial was not affected positively or negatively by financial considerations. The remaining trials faced not inconsiderable financial difficulties. These were addressed in a number of dynamic ways. The trial teams acted to prevent financial difficulties destabilising their trials, and also intervened successfully to address financial issues as they arose.

### **Securing multisourced funds**

The four trials had different paths to achieve their funding, and this related in part to their initial choice of funder, and in part to their differing costs of and responsibilities for treatment.

The MRC usually funds research in the 'response mode'; that is, the research idea originates with the applicant as the creative figure who determines the direction of the research. However, from time to time the MRC makes 'calls for proposals', which seek to encourage research in strategically important areas. In contrast, the latter approach is the norm for the HTA Programme, which seeks suggestions from the NHS and its users about possible research priorities, and then commissions research to answer those questions.

Whichever the funder, the success of the trial teams in terms of gaining HTA Programme or MRC support initially was only part of the funding process. Both the TOuCAN study and the ELEVATE trial required funding extensions to achieve their research aims.

In addition, the ELEVATE trial, HPS and the FOCUS trial all had additional funders. The PI

for one of the trials explains how complicated and delicate an issue funding can be when researchers have to deal with a number of potential sources of funding:

... trials are funded from different sources and research costs of the trial, which would be the cost of actually running the trial unit and gathering the data and doing the data analysis – that's the element of the cost for which one applies to charities or MRC. ... [We] had those costs fully met and [our] application went through without a hitch. But in any trial like this, the costs of actually delivering the treatment and doing all the other stuff that goes along with treating patients may in fact be very much larger than the actual research costs. ... There were clearly going to be issues of how we were going to obtain the drugs and get them into a trial which would involve a lot of patients in NHS hospitals around the country. ... So part of the reason why the trial took an awfully long time to, to get off the ground initially was that ... we felt that with trials like this that it was really only likely to be a success if we could get the drug companies on board to the extent that they would provide some free or discounted drugs for the trial.

For the FOCUS trial there was "a difficult and long drawn out process of negotiation" with industry and with the NHS to complete the level of funding needed, an experience echoed in HPS. For HPS these negotiations were protracted, despite initial success with a pilot study:

The idea was that we were going to do the study funded solely by [a drug company] and they supported a pilot study. ... The gap that occurred between the pilot and the main study was merely an issue of getting the funding. We had initially been thinking about a ten thousand patient study but the more we got into it the more we felt that a bigger study of twenty thousand patients would make more sense and we couldn't persuade [the drug company] to fund that ... So we spent some years pulling together the funding from a range of different sources [which] was extremely difficult. [There was] a lot of enthusiasm for doing the study from people that we collaborated with on previous trials but what held it up was just getting the money in place ... [Eventually] we retrieved the [drug company] support and got support from [another drug company], as well as BHF and MRC but it was a long process.

As these funding difficulties created a gap of several years between the pilot and the main study, there was the potential for damaging effects on recruitment and the findings of the trial. This was due to the impact of data emerging from other trials in the course of the study. One interviewee explained: "there were some types of patients in HPS for whom their own doctors wanted to use

cholesterol lowering therapy. The study would have achieved a bigger LDL cholesterol difference between the treatment groups if it had been done earlier.”

### Treatment costs

The interviewee quoted above raised the subject of different avenues of funding for research and treatment costs. Trials such as HPS and the FOCUS trial which have MRC funding should in theory be supported by an agreement with NHS trusts, known as the Concordat. Under the terms of this agreement, while the MRC covers research costs, the NHS trusts are obliged to take responsibility for ‘legitimate’ service support and treatment costs associated with MRC-funded research. Although the trialists involved in the FOCUS trial had negotiated the provision of some free drugs from industrial sponsors, the treatment costs were still described as “significant”. Trusts vary in the funds that they have available for research and, in spite of the Concordat, there were some areas where the treatment costs were not met and centres were unable to collaborate in the trial. A similar issue was faced for the ELEVATE trial, where industry was approached and agreed to meet excess treatment costs while the HTA Programme was to meet research costs. There was, however, for the three drug trials, an important matter of academic integrity which was raised by their negotiations with industry.

The senior trialists explained how they had had to maintain their own vision of the direction and focus of their research questions. They were clear that despite differing approaches to research and “very strong commercial agendas”, the industrial contributions had to be on a “no strings attached” basis:

When you negotiate with drug companies over obtaining drug supplies for trials, you usually find yourself negotiating with somebody who’s from the business unit or marketing unit of the company where, obviously, the priorities and the issues which they bring to bear ... will be commercial and business decisions. So we went through quite a difficult process of negotiating with companies ... trying to decide whether or not we could compromise on some of the questions which we wanted to ask or whether we were going to stick by our guns and potentially end up with a more difficult trial to run because we didn’t have funding. And we ended up with a trial design where we *had* pretty much stuck to our guns and where the amount of drug company funding was very much less than we might have wanted if we had compromised the design a bit more.

For the ELEVATE trial their negotiation for additional resources to fund treatment costs was essential, not only for the day-to-day running of the trial, but also to allow them to “head off the resistance we thought we might encounter from the primary health costs holding the drug prescribing budgets for primary care”.

### Staffing costs

The staffing costs for these trials varied tremendously. At one extreme there is HPS, a long-term trial involving an “army” of administrators and 69 recruiting centres, each with a funded, centrally trained, time-dedicated research nurse. At the other extreme is the TOUCAN study, a trial carried out in a local setting, and for which administration and recruitment are controlled by a small number of central staff.

For the ELEVATE and FOCUS trials, although research nurses in the recruiting centres were key members of the trial team, how they were to be resourced was a matter for negotiation. For the ELEVATE trial a contribution was made to the practices to cover the research time contributed by the practice nurse. For the FOCUS trial, although payments were made to the recruiting centres to contribute towards nursing costs, some of the costs were absorbed by the centres, and decisions had to be made locally as to how to manage this situation. In one centre resources were provided through R&D funding systems, and in another, nursing costs were met via industry links to provide protected nursing time for the trial. In comparison to the payments made to recruiting centres for their contributions to industrial trials, the income from academic trials can seem to be less than lucrative, as discussed by a member of staff at a recruiting centre:

We have a commitment to the MRC trials first. We would always recruit to them before an industry sponsored one. But that’s because we’re an academic department. If you’ve got issues of paying research nurses’ wages and you’ve got a study that pays five thousand pound per patient or one that pays two hundred pound per patient ... ! But we’re quite lucky because we have a huge patient catchment, so we’ve never got a problem in finding patients for any of our studies.

This raises an important question of competition between industry and academic trials, a factor which was likely to shape the ability to collaborate with academic trials for smaller, less well-resourced departments. Competition for patients was also an issue for the ELEVATE trial (see section ‘Key stage 2: Recruitment processes’, p. 37).

There were, however, also some feelings of optimism about staffing issues to permit trial collaboration. As one collaborator in the FOCUS trial said:

Now this is improving again ... with the NCRN, we've got 12 nurses now and some data managers. And so it actually does make it easier ... there is a definite improvement, even though things aren't as you would wish, because there are still too many patients. But it's definitely a good start.

### **Financial implications for collaborators**

Where trials may involve costs to collaborators, this can be "the final straw" in decisions about joining a trial. This is a particular concern for trials in general practice. The ELEVATE trial worked to avoid costs to their collaborators. In a highly pressured context it can not only be irksome for GPs to feel that they are used as an unpaid extension to a research team, but also result in poor levels of recruitment. A GP explained the nature of the problem:

People forget that general practices are actually small businesses and they are funded in a completely different way to hospitals. ... If you are a teaching hospital there may be funding in the system for the idea of supporting research. In general practice research is not a core thing that is funded at all. ... Even things like sending out letters, stamps on envelopes and secretarial time, all of that costs money. The only place that that money will come out of is the practice profits, which is basically the partners' income, so unless it is adequately funded you are actually asking the individual GPs to take home less money in order to do the research. That is just not the case in hospitals. It doesn't affect the doctors' or nurses' incomes at all [if] research goes on. ... In a lot of practices that is a big barrier. Unfunded research is a real problem.

As the ELEVATE trial was developed by GPs, in consultation with GPs, there was sensitivity to the need to protect practices from any costs arising from their collaboration. The trial team reacted swiftly to early recruitment problems and radically modified their administrative procedures, directing the workload away from the practices. This required greater human resources than previously anticipated. Additional funds were given by the HTA Programme to introduce new members of staff and to pay for occasional use of independent agency research nurses, thus providing the necessary support to the practices. This changed the requirement for the practices to carry out time-consuming searches, and the entire way in which potential participants were identified and recruited was refined. It was mentioned by

nurses and GPs alike that without this intensive input from the trial team, the trial would have been impossible to carry out.

In addition to a contribution to primary care trust (PCT) prescribing budgets, the practices that collaborated with the trial were also given a contribution to their funds to cover nursing time, something that was thought to be likely to promote "a stronger collaboration". Although one GP argued that this did not cover the costs involved, it was still widely viewed as an effective and essential strategy. The aim was largely to keep the costs of collaboration "neutral".

The potential for some costs to the practices was possibly counterbalanced by one particular financial benefit of the trial. One GP spoke very clearly of the balance of any cost to a practice of participation in the trial and the benefits of accessing assistance with some of the more difficult asthma cases. In accordance with their NHS contracts, GP practices are required to demonstrate that they have improved the management of such cases, and this can be a lengthy, labour-intensive process. The trial could therefore be seen as an important opportunity for hard-pressed professionals to gain assistance with this difficult task, and for their asthma patients to access a greater degree of support and nursing time than would usually be offered.

Clearly, the possibility of costs to collaborators can be a deterrent to initial involvement in a trial. For the FOCUS trial this issue had been addressed at an early stage and the cooperation of the collaborators had been secured, but a potential threat to that relationship arose at a later stage. Halfway through the trial one of the drug companies withdrew its support, with the result that treatment costs would subsequently need to be absorbed by the collaborators. Although this was very worrisome, by this time the trial, its community and treatment patterns seem to have been sufficiently established that it did not impact upon recruitment:

- Respondent: We thought this was going to be an absolute disaster, and nothing happened. Nobody really bothered; they just kept on accruing to the trial.
- Interviewer: So the hospitals were basically paying to recruit people into your trial?
- Respondent: Well yes, you could say that, although outside the trial they were probably getting exactly the same treatment.



Interviewer: And that still didn't affect recruitment?  
 Respondent: It didn't affect recruitment.

### **Key stage 2: Recruitment processes**

Once the engagement of more senior collaborators had been secured, and appropriate financial support for the trial and the recruiting centres established, another tier of professional involvement was introduced to the trials. Whereas the TOuCAN study used central trial team recruiters, recruitment to the other Part B trials relied heavily on the cooperation of nurses in recruiting centres. Some of these nurses were in existing posts and took on additional responsibilities for the trials, and some were employed specifically for the purpose of recruitment. The nurses also took on the role of motivating and reminding colleagues about recruitment issues for the trials in which they were involved. The processes involved in recruitment show how the different teams have considered factors that are likely to affect participation in their particular settings.

The TOuCAN study maintained tight central control over the process of recruitment, an approach that in part was driven by an understanding of the complications inherent in dealing with their target population of adolescents affected by anorexia nervosa. Recruitment was predominantly carried out by a small number of non-clinical research assistants who became very experienced in talking to prospective participants and their families over the course of the trial.

The protocol suggested that the trial team should be alerted whenever CAMHS received a new referral of anorexia, before the professionals involved met with the young person to make a clinical assessment. The aim was to retain central control over the information given to potential participants, and to avoid establishing a therapeutic engagement at a local level. Such an engagement may have made the adolescents or their families reluctant to consider care in any other location, thus increasing the chances of refusal to participate in the trial. It may also have complicated the experience for those allocated away from local care.

Once the trial team had been given contact details, a researcher visited the family to describe the trial and take consent if they wished to enrol. As the adolescents had reached a point where they were being diagnosed with the condition, they were already at quite a serious stage in their illness. This could shape both the tone and

management of the discussions about trial participation. Although there was a widespread view in the interviews with clinicians that the population available to the trial was predominantly middle-class, high-achieving, teenage girls, who responded to the interest shown by the trial team, those who made the home or hospital visits for the trial described some situations in which it was very difficult to engage the adolescents in conversation. Among the younger patients, or those hospitalised or eating and drinking very little, poor levels of concentration or responsiveness could be significant issues. There were some initial anxieties about random allocation of treatment in this context and the response of the team reflects an understanding of what is feasible against the backdrop of a condition such as anorexia nervosa. Where adolescents felt uncomfortable they were told that they were not obliged to accept the allocated treatment, an approach that would not often be encouraged in other trial settings. They were, however, asked to go along to the service to which they were allocated for an assessment and to learn more about what was on offer. If possible, the team tried to encourage participants to try the service for a 6-week period before choosing to swap to one of the other treatments. If they were still unsure, or if they declined randomisation, there was the option of allowing data collection in a naturalistic arm (essentially a patient preference arm) of the trial. This approach to recruitment, as well as the inclusion of the naturalistic arm, offered patients who did not wish to have control taken away from them an important expression of autonomy.

This form of patient preference trial was described as "a compromise between a pure RCT and a naturalistic study" and was driven by an understanding of the likely resistance among anorexic patients to a more rigid approach. The intention was that in permitting a degree of clinical and personal autonomy that might not be tolerated in trials in other settings, the chances of professional and patient participation in the trial would be increased. These strategies appear to have worked as the TOuCAN study is following up over 90% of the local cases of anorexia nervosa, with 78% of these randomised and 22% in the naturalistic arm. Cross-over between the randomised treatments arms was 33%, which was less than originally feared.

In the ELEVATE trial and HPS, responsibility for the recruitment processes was shared between the central trial teams and collaborating centre nurses.

The trial teams controlled the labour-intensive procedures involved in trawling records and databases to identify and book clinic appointments with potential participants, and then passed recruitment over to the nurses working at a local level. For HPS, these nurses were employed in each collaborating centre specifically to work on recruitment to the trial. They were trained by the central trial coordinating centre and were then given a high degree of local autonomy. It became their responsibility to find office and clinic space for recruitment and they regulated their own time. For the ELEVATE trial, the nurses were largely existing practice nurses who took on a commitment to recruitment as part of their general duties, for which the practices were reimbursed. Where a practice was not able to supply a nurse, the trial team employed four independent agency nurses who were occasionally placed in a practice to recruit to the trial. The more senior collaborators in the two trials who had permitted the research to run in their centres had a minimal role in recruitment, although opportunistic recruitment, often at the prompt of the research nurses, could take place via their own caseloads.

The patients who were eligible for the ELEVATE trial were those with poorly controlled asthma. During the course of the trial, a competing commercial drug trial was established. Potential participants for this trial were, in the opinion of two of the interviewees, often those who were easier to recruit, and their recruitment elsewhere had implications for the ELEVATE trial. Not only was the available population reduced, the perceived characteristics of the remaining population was thought to have shaped, if not complicated, the process of recruitment in important ways. A number of interviewees made the point that these remaining patients often did not define themselves as having asthma; rather, they felt that they had some breathing difficulties for which they had been prescribed an inhaler. It was more difficult to persuade such patients of the relevance of the trial to their situation, and accepting the offer of recruitment could mean accepting a (possibly unsettling) status as an asthmatic, with implications for required drug regimens. The asthma symptoms for some patients were poorly controlled as they were not compliant with their prescribed medication. They often did not attend for monitoring and they were a difficult group to recruit. Given the difficulties associated with this population, the trial team made enormous efforts to track down as many potential participants as possible.

Once patients had been identified, similar recruitment procedures were used by both HPS and the ELEVATE trial. Clinic appointments were made by the central teams with patients (in itself a time-consuming process which, for the ELEVATE trial, included calling many potential participants at home in the evenings and weekends), at which they would be assessed to confirm eligibility for the trial. The nurses were responsible for informing patients about the trial and for taking consent from those wishing to join. For both trials the recruitment procedures involved several appointments and typically took place over a 6-week period for the ELEVATE trial and an 8-week period for HPS.

For these trials, the clear delineation of responsibility for identification and recruitment of potential participants was given by most of the local health professionals as a condition of their agreement to collaborate. This was not surprising as the process of identification for both trials was daunting. It was estimated that just for one large general practice, the ELEVATE trial team identified and wrote to 800 patients in order to bring 30 to the clinic. For HPS, the trial team wrote to 131,000 patients and screened over 63,000 in the recruiting centres to achieve their sample of 20,000 participants. This extraordinary effort at a central level made the collaborating centres' own involvement far less onerous, allowing the nurses to concentrate on screening and recruitment. The collaborators who were interviewed were well aware of the value of the central identification processes and of having protected nursing time for recruitment. One of the HPS interviewees commented on how the system of recruitment was crucially important for his centre, both in terms of allowing sufficient time for the trial processes and for protection of his own time and duties:

The nurses go down to Oxford, they're fully trained, they know how to organise the clinics, so my involvement in these clinics was minimal. ... When we were recruiting the patients ... I was required to put my signature on the forms, but that was very much a rubber-stamping job. ... If it was in competition with our service commitment, it would very quickly be sidelined and we wouldn't be able to do it.

This point was made repeatedly by recruiting centre staff for HPS and ELEVATE and was well recognised by the trial teams; one member of a trial team described how they had come to recognise that in order to promote recruitment it was important that their own research teams should do "all but the most minimal of processes".

For the FOCUS trial, both identification and recruitment of participants were entirely under local control. It was usual for a member of the clinical oncology staff to identify eligible patients. A consultant would initially explain the trial to the patients, usually in the context of discussion of the management of the advancing nature of their disease. A research nurse would then give further details of the trial and arrange to see the patient again some days later, to take consent and initiate their therapy if they wished to enrol in the trial.

The collaborating centres were given a contribution towards nursing costs which allowed for some protected nursing time, but the centres appeared to vary in the level of resources that were available. The nurses who were interviewed had a strong identity both as oncology nurses and as research nurses, and this was reflected in their approaches to recruitment. The process of recruitment to the FOCUS trial could involve several appointments if the nurse felt that the patients were overloaded and needed more time to understand or to consider their decision. This was important as it could involve patients who had only just learned that their disease was inoperable. It was very clear that despite their own commitment to research generally and to the FOCUS trial specifically, the research nurses did see themselves as having primary responsibility to the patients. The decisions that patients were asked to make were in the context of the last months of their life and so the nurses felt that they needed to draw on their own professional experience, and on “wider nursing issues”, to assist this potentially rather vulnerable group through the trial processes. It seemed to be important to the nurses that recruitment was carried out in a supportive, patient-centred environment. The fact that it was governed locally appeared to offer nurses an important sense of professional autonomy, in which they were free to exercise their own values. One nurse argued that the nursing perspective was rather different to that of the doctors and this may shape who enters a trial, as well as the style of recruitment:

If a patient were to come to a clinic, and the consultant or doctor [said that] this person would be feasible to go into FOCUS, say if they'd already had chemo in the past, or they might not be fit and well, the medical staff might view it a bit differently to how we would. We might think they're not suitable to go into a study. I think a lot of the time we're looking at things from a different perspective, perhaps we're looking at things more as an advocate. And although we are there to recruit, we're also there to protect the patients. ... They [can] be quite a vulnerable group.

Another nurse explained how the discussion of recruitment to the trial was potentially shaped by both the type of patients and the “emotivity of the disease”. Although among the target population of patients with advanced metastatic bowel cancer there is a bias towards older patients, there are some younger patients and she argued that these two groups approached both their disease and the trial very differently. This meant that they needed a different type of input from their research nurse:

[The older patients] are not quite as inquisitive as the younger generation, and probably not as fearful. ... And maybe there's something to do with their perception of the nursing and the medical profession. They have still got that [view] that the doctor's the be-all and end-all, and you [accept] everything what the doctor says, and that lovely nurse type of thing. You try to get away from that, [saying] 'This is about you. You've got as much right to make a decision'. But the elderly population do hold everybody in a much higher regard. ... The younger age group ... are more fearful, more frightened about the situation they're in. They might have a young family and things like that. You have to usually put a lot more in with them, because you've got to get past the diagnosis, you know, help them with cope with the diagnosis before you go onto the treatment.

Clearly, in recruiting to the FOCUS trial the nurses were required to draw on their professional skills to manage a particularly difficult situation. Their degree of specialism, in terms of both their understanding of research and of the patients' needs, seemed to produce a very careful and measured style of recruitment.

### **Key stage 3: delivery of care**

Concern for patient welfare and for the impact of trial participation on patients has been shown to be a major obstacle to professional involvement in trials in a number of studies. There have been trials that have caused a degree of professional anxiety;<sup>41</sup> professional non-participation<sup>72,73</sup> or non-compliance<sup>34</sup> can ensue if the treatment allocation is not thought to be in the patients' best interest. Recruitment, retention and patient compliance may all be affected in trials that are designed with insufficient sensitivity to patients' concerns or needs,<sup>74</sup> and trials where patients may prefer one arm can be particularly difficult.<sup>75</sup> It therefore seems likely that protecting patient welfare may well be a factor in promoting recruitment, through maintenance of professional confidence and patient satisfaction. The quality of care offered in the context of the Part B trials, and the subject of what the trials were thought to offer patients, were therefore explored with the interviewees.

The discussions tapped an important area of professional interest and often took a substantial portion of the interview time. It was clear that high standards of patient care within a research framework were particularly valued and the interviewees for each of the four trials largely conveyed a sense of professional satisfaction with the care offered to their own patients. This possible impact on the delivery of care in the context of the Part B trials can be examined in the context of attitudes to the interventions offered in the trial, and the perceived effect of association with the trial on care for patients and for clinical practice.

### **Impact of the trial interventions for patients**

The interventions being tested in the four trials were statin therapy and vitamins (HPS), chemotherapy agents (FOCUS), asthma medication (ELEVATE) and packages of inpatient and outpatient psychiatric care (TOuCAN). HPS was the only study to include placebo. There was a degree of optimism expressed in the interviews that the interventions would prove to be effective and that the trials therefore constituted a means of accessing a potentially helpful form of care. Perceptions of the importance of the individual treatments themselves were, however, quite different. In the interviews with staff involved in the ELEVATE trial, for instance, there was less discussion of the possible impact of the drugs involved, and more interest in the delivery of nurse-based supportive care, which was the same for both groups. A similar issue pertained for HPS, even though the trial has reported very persuasive results. The two trials in which the interventions under consideration were thought to have a greater impact on patients were the TOuCAN study and the FOCUS trial.

The planned use of randomisation to determine the care offered in the TOuCAN study raised varied responses among the community of professionals in the development stage of the trial, as described in 'Key Stage 2' (p. 37). As this group held sway over referrals to the trial, their perceptions of the possible impact of the trial treatments for their patients could be an important determinant of recruitment. The consultants who had referred their patients to the TOuCAN study were, however, relatively at ease with the different treatment options, seeing both advantages and disadvantages to inpatient and outpatient care. All described the professional stresses inherent in dealing with anorexia nervosa, with sleepless nights and much anxiety, but they did not suggest that any possible impact of the

different treatments considered in the trial caused them particular concern. One commented "I am fairly comfortable with it all really". The allocation process seemed to be tolerated even where the professionals had a degree of preference in one direction or another:

I'm uncertain about the place and benefit, particularly of long inpatient admission, so would always be inclined to have a go at kind of motivational outpatient treatment first. So having to refer people on [at an] earlier [stage in their illness] has been frustrating, [but] worry is too strong a word.

When another consultant described a preference for community rather than inpatient care, he was also asked whether allocation of patients to inpatient care caused him concern:

I don't mind if they try [inpatient care], I'm interested to see what happens. I've got enough people to worry about without getting too worried [about that]. I'm not one of the sort of anxious rather conservative people who [is concerned that] the trial might have stopped me having a hospital admission [because] you don't get them much anyway. And I know I could twist people's arms when I want to.

There was an important strand in the interviews which indicated that at times the ability to use the trial as a means of strategising the care of the most difficult cases, with the possibility that they would in fact be randomised on to those with greater experience of care for problematic patients, could be "an absolute Godsend", "a relief to get a difficult case off your mind". One clinician thought that some professionals who are particularly "embattled" would be "delighted to have a trial to refer to" as it offered "an opportunity to get people a more expert treatment than they would've done otherwise". Another interviewee explained:

The children concerned often cause a great deal of professional anxiety because they can be physically very ill as well as psychologically ill and so they might be few children but [they are] very worrying children. There may be an element that the team felt that it was helpful to be plugged into a centre of excellence and to be able to draw on that expertise. I could imagine there would be some departments which are much smaller and less well-resourced where they'd be very grateful for the chance to pass some of their children on to a centre of excellence.

It was notable that they presented the patients and families within their care as being very much individuals with different needs. For some patients

and families, inpatient care could be difficult, while for others it was seen as offering a valuable opportunity to provide some space between adolescents and their families. The degree of flexibility afforded to the families and professionals through the opportunity to decline or override the allocated treatment seemed to be essential. It was also suggested that the treatment options within the trial might in fact be in greater harmony with the views of the families than with the professionals:

These families often have a belief in inpatient treatment and distance centres and specialist centres and so sort of the idea that two of the three options are actually specialist options is consistent for these families with what they think they want.

The professional views of the impact of the treatments available in the FOCUS trial provide quite a contrast to those just described. Although there was recognition in the interviews that cancer patients do have differing needs, and will make very personal and individual decisions about the care that they wish to receive, trial enrolment was largely seen as offering access to drugs that were widely thought to be potentially very helpful but were otherwise not readily available.

This became a hugely important and quite complicated issue for the FOCUS trial. The publication of guidelines restricting the use of irinotecan and oxaliplatin by the NICE in 2002 (see 'Results', p. 26) was highly contentious. Practitioners now faced restricted access to what were seen by some as "cutting-edge" drugs, and the FOCUS trial was established as the main access route for oxaliplatin in the UK. The NICE debate also brought to the fore discussions about the differences in availability between the UK and other parts of Europe and the USA, with the acknowledgement that patients may learn of the existence of drugs but then be given the potentially demoralising information that access in the UK is restricted.<sup>76</sup> It should be noted that it was not impossible to access these drugs as they are licensed for use in the UK, but there are important prescribing costs to be considered that could effectively prohibit their use for many practitioners. A nurse described how she presented this situation to patients when offering participation in the trial, trying to balance information giving with avoidance of stress and pressure in an already difficult situation:

[Now] you don't want to force a patient to go into trial, but I do say that by going into the FOCUS study, there is oxaliplatin available. We don't have

funding for that outside the study. I think you have to say that as being honest with the patient; that we don't have it. But you don't want to put it in a way that 'Well if you don't go in this study, you just don't get this drug'.

There was a view that there was some evidence of efficacy from data from other trials, and some interviewees felt that there were perceptible benefits in the survival times for their existing patients:

If you don't have chemotherapy your mean survival is about six to nine months. 5FU is about 12 months. Irinotecan and oxaliplatin about 15, 16 months. And then all three of them is 20. So every little step is important. So I suppose you want people to receive all drugs, if they can, in a tolerable way.

There were differing opinions among the interviewees over the impact of this shift on recruitment to the trial. Some practitioners stated that they explicitly and deliberately recruited to the trial in order to access drugs. A nurse argued that the impact of the limitations on the availability of the drugs was probably disproportionate, with the restrictions being felt most keenly by smaller centres where funding for irinotecan outside the trial would be impossible. Larger centres did have funding agreements that made it somewhat easier to access the drugs. She suggested that it was the limitation placed on the smaller centres that probably impacted positively on their levels of recruitment to the trial. Although the issue of limited availability of irinotecan for patients allocated to three of the trial arms was of concern to some interviewees (before the change in trial design to permit cross-over), this appeared to be counterbalanced by the attraction of the availability of the restricted oxaliplatin within the FOCUS trial. A consultant articulated a sense of compromise:

At least in the FOCUS trial you could get all three drugs at some point. And so I suppose we felt that every trial isn't perfect, but even on the control arm ... they could get oxaliplatin afterwards. That trial was good for that. That's why we put patients into it.

Two consultants explained that an important attraction of the trial was the ways in which it could structure care for patients. Although the FOCUS trial is undoubtedly complicated, the design could be seen as a treatment guide, "a plan for life for patients", mapping out exactly what would happen step by step, including consideration of patients' care after the trial

period ended. The knowledge that an alternative drug would be available on progression of their disease was described as “positive” as it promoted patient confidence in their treatment. There was, however, some degree of compromise. Although all of the drugs are available within the trial, not all patients will survive to receive them. A consultant described how this was balanced with the search for a way of giving the best treatment in the most tolerable form:

If you say 100 percent of people get level one, the first treatment, actually only about 50 percent get the second level. And probably 10 to 20 percent get the third level. [You] might find that you get somebody who's fighting fit at the beginning, their disease progresses in the first three or four months, they're never fit enough to receive anything more. So there's pros and cons of it all. I suppose by giving too much treatment up front you might make their life intolerable. And so there's a happy medium somewhere there.

#### **Impact of some of the trial processes for patients**

Trials can offer more than simply the treatments in the protocol. Whereas the available literature on barriers to recruitment suggests many ways in which patient care can be affected by the offer of trial participation,<sup>15</sup> the interviewees for the trials studied here often described very positive effects of patient association with a trial.

All of the trials involved an appreciable level of human contact and patient support in their procedures. For the TOuCAN study the attention paid to the adolescents both in the recruitment procedures, which involved a visit to their home or hospital bed, and for follow-up was thought to be a very positive element of the experience. A consultant commented:

I think people have, have, quite enjoyed being part of it really. You know they do get quite a fuss made of them and, and, they get to go back for the one and two year follow-ups. I just saw someone last week who had been back for a two year follow-up and was quite enjoying that really.

For FOCUS, ELEVATE and HPS, a significant degree of patient association with the trials involved contact with a research nurse. The nurses had important roles in recruitment to the trials, but they placed their own duties very much in the larger context of their duties as a nurse. This meant acting not only as a patient advocate during the decision-making process, especially for the FOCUS trial where those considering enrolment might be feeling vulnerable and overwhelmed, but

also as a health professional with a chance to intervene to affect patient well-being.

The ELEVATE trial and HPS both involved an initial screening visit in the recruitment process, wherein potential participants underwent a number of tests and were asked questions about their health and health management. Several of the nurses commented that they appreciated the luxury of long appointments (up to 1 hour) for each patient, where concerns could be expressed and a relationship could be built up, a sharp contrast to the usual constraints on their time. For both trials the nurses said that at the initial appointments they included an extra degree of input that was not required by the study protocol, such as carrying out blood pressure checks. Some went to considerable lengths to ensure that GPs were made aware of any possible problems and clearly saw their encounter with patients as a health education opportunity.

There was reported to be an effect of the screening appointment for patients who had poorly controlled asthma who were invited to join the ELEVATE trial. It seemed that for some patients the discussion of their symptoms and asthma management promoted greater use of preventive medication (rather than simply symptom relief), and improved their control of symptoms to a point that they had become ineligible for the trial by the time of their second visit.

Not only were there benefits of patient access to a nurse, it also seemed that there was a helpful continuity of care. Participants could establish a relationship with the research nurse that could continue throughout their participation in a trial and beyond. A research nurse from HPS said:

I still see those people locally now and they talk to me and still recognise me and you know, there's still that good relationship there.

Several interviewees articulated a view in which it is in patients' best interests to enter the trial because of the broader package of supportive care. One nurse linked to the FOCUS trial clearly felt this:

I feel bad for people that don't go in it because you think, well who is their nurse if they're not on a trial, you know, who's going to be providing that extra support? ... All they get is the outpatient nurses who are really stretched and pushed themselves. So I feel [that] a lot of the time they get extra counselling and extra one on one support, which people don't [usually] get.

The ability to interact with patients not only emphasised the importance of patient care, an element that is likely to appeal to health professionals, but also de-emphasised the research element, which can become uncomfortably disproportionate in some trials in difficult settings.

#### **Key stage 4: Delivery of research**

However great the effort that is put into the development of a trial and the management of clinical elements of the research, if a trial is inefficient and its management poorly thought out, success is likely to be compromised. Delivery of the research depends on practical input to securing patient contact, implementation of trial procedures, data collection and analysis. This section considers how this key stage of the trials was conducted. It is an enormous shared task, and so it describes not only perceptions of the value of sound administration, and the ways in which motivational strategies were employed to maintain the profile of the trial, but also how those with a variety of responsibilities to the trials are brought together as a team with the aim of protecting or improving recruitment (see also Chapter 4).

#### **Teamwork**

For the TOuCAN study it was said that promoting teamwork and effective communication had been “a challenge in itself”. This was not surprising as the team structures of the trials studied here were often highly complicated. There seemed to be a number of teams within their larger frameworks. The central coordinators operate as a team, as do groups of doctors and nurses working in recruiting centres. Even where there is only one individual in a centre, either making referrals or recruiting to the trial, there was often an articulation of membership of a larger team working in a different way, but in a collective fashion, towards a shared goal. The relationships between the various individuals and groups were important, creating what was described in one interview as “the chemistry of the team”:

Key factors in success are having a good group of people who really can figure out what their roles are. Communicating well and fulfilling promises. [Central team members need to] understand [recruiting centre staff's] perspectives and their concerns.

If individuals do not fulfil their professional commitments to other team members or to the trial, and in turn are pressured or irritated by requests for action, a trial is unlikely to run smoothly. Here the interviewees often mentioned their colleagues within a trial team very positively.

The centres felt supported by the central teams and frequently said that they were given prompt answers to any queries. A GP involved in the ELEVATE trial contrasted his experience of this team with that of another trial:

I think that the most important thing has been the support from the researchers [and] the infrastructure that has been provided. ... I contrast that with a study I was doing for a commercial research organisation which was overly burdensome with paperwork [and involved] very poor support from the research assistants. In the end we didn't recruit anybody for their trial.

Working as a team is not, however, something that happens naturally. It requires particular input from those involved to maintain and regulate their own and others' positions within the trial. One interviewee argued that without clarity over roles and expectations of team members, a trial is likely to fail:

A recipe for a failing trial is to have a committee designing a trial with a weak PI who isn't 100 per cent committed and who leaves the trial office to do the work.

Multicentre trials are dependent for their success on the contributions made to recruitment by those who are, more commonly than not, volunteering to work on their trials. As described above, the central teams worked to create a sense of commitment and loyalty to the trials through building relationships, giving information and addressing concerns. The training sessions and clinical meetings that were offered to all collaborators for HPS appeared to be particularly effective on all three fronts.

The expertise of trial managers and the inspiration of PIs were highly valued. It was common for interviewees to describe the contributions made by particular individuals. In one trial, central trial team individuals had been chosen specifically to complement the profile and skills of the others, mindful of what this would offer to the local teams and their patients. The PI described how the role of one, a doctor, was to bring on board fellow doctors through academic and shared professional appeal, and of the other, who had a lot of experience in working with health professionals, was to act as a diplomat, to “charm” patients and professionals alike.

#### **Administration**

The administrative workload for a trial can be extremely heavy, as demonstrated by each of the

Part B trials. This is especially the case where centres require a high level of contact and support, as in the TOuCAN study and the ELEVATE trial, or where there are many centres involved in recruitment. HPS faced a particular administrative challenge, with a large number of recruiting centres and a long timescale. Interviewees from the HPS centres commented on how well thought out all trial procedures and documentation were, and how impressed they were with the trial organisation. Careful planning and the development of strategies to manage the administrative load involved in patient contact and recruitment were seen by some of the administrative staff as essential for the trial. An important factor in this area of success, as with the FOCUS trial, appears to lie in the location of the trial team within a larger professional clinical trials unit, centres with a reputation for expertise in the conduct of trials.

Although there could be a lot of central assistance, some of the administrative load, especially provision of follow-up data, fell to the recruiting centres, and this could cause difficulties. In one FOCUS trial centre, recruitment to the trial had slowed down as the backlog of data collection on previously recruited participants had become unmanageable. For some months patients were treated with standard care rather than recruited to the trial to allow local staff to try to regain some administrative ground. Funds gained locally from industry and from R&D were used to fund nurses and data managers for the department, and one nurse was specifically appointed to address this backlog. The centre was then able to pick up recruitment without the concern of a high administrative load building up. The difficulties created by this backlog were mentioned by several interviewees. One nurse felt that this situation would not have arisen for an industry-funded trial. She argued that where nurses' salaries are funded by industry, there is an expectation that they will fulfil an obligation to meet data collection requirements, and these are more stringent than in academic trials. It was felt that for academic trials, stricter monitoring combined with appropriate support was desirable to keep busy centres on track.

#### **Motivational strategies**

The trials all used standard motivational techniques such as newsletters, *aide-mémoires* and competitions for the highest recruiters. There were two approaches that seemed to be most effective, according to the interviewees. The trials commonly held meetings for professional

collaborators (HPS also held them for their patient participants), and these combined educational and social elements. They served to improve interest in and knowledge of the trials and aimed to promote a sense of the trial community. The trial team also often fed back recruitment figures so that centres could compare their progress with that of others involved in the trials. This could stir a competitive spirit, particularly in larger recruiting centres with the potential to bring in more participants.

Some of the motivational work was carried out locally by those with a sense of investment or ownership of the trial. The nurses who were interviewed from the ELEVATE trial were well motivated themselves and placed a lot of emphasis on their own ability to influence ad hoc recruitment. This could be by encouraging and reminding the GPs in their practice to be alert to the eligibility criteria for the trial when they are consulting patients, or it could be nurses checking records themselves. One nurse sent regular e-mails to her colleagues as reminders and described herself as "prompting them the whole time". Even though the majority of the patients enter the trial by way of the standard identification processes for the trial, rather than through ad hoc recruitment, the value of an enthusiastic nurse was appreciated by the trial teams.

For the TOuCAN study the success of the trial depended entirely on the cooperation of the CAMHS professionals, and therefore much effort was directed into promoting their participation, maintaining the trial profile and trying to ensure that referrals of new cases of anorexia nervosa were not missed. There was a policy of frequent contact and each team was telephoned on a monthly basis to check for new referrals. Newsletters and other *aide-mémoires* (bookmarks, postcards and Christmas cards) were used, as well as an annual census of all cases of anorexia in which the teams were asked to state whether or not they were referred to the trial. Practical assistance with caseloads was also offered to promote involvement with the trial, in that those with a long waiting list for clinical assessments could take up the option of passing over assessments to the Eating Disorders Service at Chester. To maintain good relations, the team observed a policy of always providing prompt feedback on decisions about participation and the allocated treatment to the CAMHS team for each patient seen by the research team. This was mentioned as something that was much appreciated by one of the CAMHS interviewees. When new consultants join CAMHS



teams, the trial staff make contact to establish a relationship and to make sure that they are aware of the trial.

### **Common factors in the successes of the Part B trials**

The four Part B trials have essential internal differences in their aims, settings and methods. During the course of the trials they have also been shaped by external factors, such as the NICE guidance on treatment for colorectal cancer patients for the FOCUS trial, and competition from another asthma drug trial for the ELEVATE trial. Given their intrinsic and extrinsic differences, the identification of any possible common factors in their success may be useful in terms of the light shed on the running of other similar and dissimilar trials.

These factors are considered initially in two ways: first, an analysis of themes from the key stages presented above where the common factors cut across at least three of the trials, and which appear to offer insights that may be used elsewhere; and second, from the responses of the interviewees to the specific question that asked them to explain which factors they thought were the most significant in the success of their trial. These two methods for considering factors in success are then contrasted and compared.

### **Common factors in the successes of the Part B trials based on analysis of themes identified in the key stages**

As might be expected, analysis of the themes showed that success was thought to be related to the clinical importance of the research question, and confidence that the trial design was scientifically sound. This appeared to be closely linked to perceptions of the PIs, who were seen as responsible for the design and direction of the trials. They were respected not simply as high-profile academics, but because they were, for instance, “an OK bloke” or “a good doctor”. They were seen to have conviction and to be resolute; one was thought to “never waiver” in his commitment to the design of the trial.

In addition to good-quality science and leadership, it was clear that the interviewees in all four trials considered that the ‘processes’ involved were key factors in the success of the trials. They pointed to the considerable time and effort taken in getting the foundations for their trials well established, and felt that this was effective and time well spent. This process of laying the groundwork (although facilitated if there was a

pre-existing network of experienced trial collaborators or an established trials office) helped to instil a strong sense of commitment to the trial, regardless of the original climate.

Although the trials varied in their approach to the recruitment processes, there was a common sense of their accommodation of the needs of potential recruits, such that clinical collaborators felt able to fulfil their own sense of obligation to their patients, and that the trial was firmly grounded in their own clinical practice, and so may be useful in their practice after the trial.

Expertise for the trials was fostered through various forms of training, and hence participants generally appeared to feel well informed. There was appreciation from the collaborators that they were protected from some of the workload associated with involvement in a trial, for instance by having dedicated research nurses, and that responsibilities within the trial were well delineated within an efficient management system.

The interviewees identified themselves as part of a successful, hard-working and motivated team, and this feeling bred greater success and confidence, such that they were able to adapt to and overcome even serious problems such as funding crises and NICE pronouncements. What interviewees in all of the trials seemed to be pointing to was a climate in which there was an important sense of collectivity operating, where central teams and collaborators were enthusiastic and keen to make their trials function well and to “deliver”.

### **Factors identified by respondents as the most significant for the success of their trials**

When, at the end of the interview, respondents were asked what they felt were the key factors in the success of their trials, they were not given a list of possible factors from which to select or any other form of direction or guidance.

The responses for each trial are shown in *Boxes 1–4*.

It should be borne in mind that the interviewees had already talked about many aspects of the trial in the course of the interview and so may not have repeated some of what they had already said was important for success. It was noticeable that although respondents from the central trial teams did select some different features of their trial to mention, compared with local collaborators, there was no evidence of strong disagreement within a trial about the trial’s success and the broad reasons for that.

- Important/interesting research question (×2)
- Good design, good protocol
- Clinicians keen to recruit to trial
- Drugs already tested so easier to explain to patients
- Didn't demand extra effort from patients
- No competing trials for those centres/patients
- Approval from NCRN
- Centre accreditation
- Drugs not available outside the trial (×2)
- Excellent trial management
- Good communication between trial team and clinicians
- Trials unit helpful, caring
- Good public relations/feedback/updates/information for collaborators (×5)
- Annual meetings for all concerned
- Trial steering group played an important role in defending the trial

**BOX 1 FOCUS** (comments from ten interviewees)

- Flexibility of trial team and flexibility allowed to practices (×3)
- GPs involved in design (academic GPs) and practical side (active GPs)
- Trial team able to see things from GP perspective
- Pragmatic study
- Good design
- Good funding
- Practices not 'researched out' already; not too stressed; enough willing to take part (×3)
- PI well respected
- Trial run by good team, good infrastructure (×3)
- Trial team communicative, responsive and alert to problems (×3)
- NHS funding and contact through GP legitimise the trial for patients
- Patients have done well with their asthma control
- Impact on practice running and costs was minimised (×2)
- Role of research nurse

**BOX 2 ELEVATE** (comments from 12 interviewees)

- Communication within team and between team and collaborating clinicians (×7)
- PIs worked hard to keep collaborators on board (×3)
- Topic important, urgent need for research (×2)
- Trial good for local staff because it gave them training, motivated them and improved their working relationships (×4)
- Good trial team, responsive, good research assistants (×4)
- Study included everybody
- Team worked hard at how to explain the study to patients

**BOX 3 TOUCAN** (comments from ten interviewees)

- Good planning and organisation by CTSU
- CTSU responsive, efficient
- Central organisation of many aspects of the research
- Minimising work for health professionals
- Agreement in principle from GP to approach patients
- Prior screening to make sure patients were eligible (×2)
- Important question, timely and managed to roll several questions into one study

**BOX 4 HPS** (comments from six interviewees)

**Common factors identified by respondents as the most significant for the success of their trials**

In their summing up, some features were mentioned by respondents across all four trials. The most obvious were good communication between the centre and local collaborators and an efficient and responsive centre. In two of the four trials (ELEVATE and TOUCAN) interviewees described a close identification between the PIs and the collaborating clinicians. In TOUCAN the work done by the PI in keeping in touch with local clinicians was specifically mentioned. In ELEVATE it was clearly very important for the participating GPs who were interviewed that the trial was designed and run by GPs. In a third trial, FOCUS, a parallel set of comments was about the value of involvement with a respected trials unit and approval for the trial from NCRN. Another important common feature of these trials that was mentioned by interviewees was that they were designed to minimise the burden on local collaborators (HPS, ELEVATE) or that participation had benefits for those who took part (ELEVATE, FOCUS, TOUCAN). Benefits included improved local team working, access to training and meetings and benefits to patients (in ELEVATE) because of extra attention to their asthma.

The importance, interest and timeliness of the trial question were mentioned in three of the four trials (not ELEVATE), and good design was mentioned in two. Specific design features that were mentioned as encouraging clinicians or patients to take part included drugs not being available outside the trial (FOCUS), NHS funding and contact through a GP legitimising the trial for patients (ELEVATE), and being able to say to patients that their GP approved in principle of an approach to them (in HPS).

## Common factors in the successes of the Part B trials: summary

Common factors emerged both from analysis of the broader interviews and from the specific summary question.

From both sources it was clear that a key feature was the importance and timeliness of a research question that had the potential to lead to real changes in practice. Alongside this was a view that a trial design that put respect for the needs of patients and the clinical professionals within the trial at its centre was likely to be successful.

These were seen as necessary but not sufficient conditions. Respondents also saw the leadership role of the PIs as crucial, particularly in terms of their standing in the clinical community. However, they all recognised that the clinical leader needed to be backed by a strong and efficient coordinating team, which was able to take much of the weight of participation in the trial off the hands of busy clinicians, and yet use excellent communication skills to keep all the collaborators on board, well informed and enthusiastic ambassadors for 'their' trial.

## Discussion

This component of STEPS has complemented the approach from Part A. Rather than using a quantitative approach working with documentation provided for a large number of trials, four trials were looked at in more detail using a qualitative approach. Chapter 5 compares and contrasts the findings from the three STEPS parts. In the rest of this chapter, the conclusions of Part B are discussed in the context of the strengths of this method and also its limitations.

The available literature is large and complicated with a lot of methodological variation, but it does point to a number of potential barriers to recruitment for professionals. The data from the interviews described the efforts that teams in these exemplar trials made to address, adapt to, mitigate and even prevent the effects of these potential obstacles from affecting recruitment rates. It may have been significant that these trials were not simple and easy trials, but faced considerable challenges. Where the larger trial teams were aware of the difficulties inherent or the obstacles overcome, this seemed to increase respect and motivation.

A specific aim of this research was to gain insights into facilitators to recruitment that are likely to be relevant to trials in general. Interviewing individuals in several trial centres with a wide range of responsibilities, and the exploration of key stages for the four Part B trials, suggested a number of factors that seemed to offer useful lessons and that might be replicable. The interview process itself conveyed something of the culture of each trial and offered the opportunity for insight and reflection.

The common key factors identified by the interviewees suggested that high research standards are extremely influential in their experiences. This would make sense because if researchers and collaborators are to invest their time and effort, not to mention exposing patients to a trial, then they need to feel confident and motivated and that a trial is 'morally right' to offer. The discussions for this study suggested that high research standards were, however, greater than simply a good question or a scientifically robust design. Professionals appeared to be most enthused by a sense of contributing to research that they perceived as having the potential to change their clinical world, and that was sensitive to the needs of patients and professionals alike. The PIs were highly important, as inspirational figures at central and local levels.

These trials also showed how much attention they paid to getting the foundations right. To the authors' knowledge this aspect of trials management, and the contribution that it makes to subsequent recruitment, has not been previously described in the empirical literature.

The various factors explored here may be tightly interrelated, and what is expressed in forms such as "a good team", "hard work", "good communication" and "organisation" do tap in to a more general ethos, a spirit of enquiry carried out with a high degree of professionalism. Indeed, this was evident in the often striking degree of cooperation offered to the researcher. This sense of dynamism, clarity and efficiency extended to the conduct and content of the interviews. There were strict time constraints for Part B and so requests were often made with a degree of urgency. They were met with prompt and efficient replies to queries and provision of comprehensive and clear trial material. Some trial managers went to considerable lengths, writing long e-mails to ensure that the relevant issues for their trials were made clear. Not only did the interviewees give of their time, it was clear that many were deeply

committed to their research, as reflected in their patient descriptions and enthusiastic engagement in the issues raised in interview. Although it is difficult to quantify the impact of this quality of commitment on recruitment, it is likely that a culture of motivation, responsiveness and commitment that prevails at different levels, both centrally and locally, will be a positive force and a contributory factor in the success of a trial.

The conclusions from these interviews must be tentative. This study focused on a small number of trials and although these covered a range of specialities, interventions and trial designs, it is likely that more might be learned by extending these interviews to a larger number of more diverse trials. The authors chose to concentrate on exemplars and these particular trials were

suggested to them by the funders. If we had, instead, chosen trials that had achieved their target recruitment within the originally agreed time-frame, further insights might have been gained.

The interviews elicited perceptions of the reasons for the success of the Part B trials. It is plausible, however, that if interviews had also been conducted with teams within trials that were not exemplars in either sense, the study might have found similar factors operating.

However, it was clear from the interviewees that they did see themselves as members of successful teams. The ways in which trials are organised and how teams operate are ripe for further research and are explored in the next chapter.

## Chapter 4

# The clinical trial as a business: a single, in-depth case study of a large multicentre trial

### Introduction

The in-depth case studies of four trials in Chapter 3 suggested that management and teamwork play important roles in a successful trial. However, many, perhaps most, clinical trials are devised, managed and reviewed by clinicians and allied professionals only. This is not surprising since the purpose of a trial is to advance clinical practice. However, could it be that conducting a successful clinical trial requires activities that disciplines other than medicine are best suited to deliver? In this chapter it is suggested that clinical trials can be seen as businesses and that the disciplines of business management may be relevant to those who conduct clinical trials.

Businesses find customers and convince them to buy what is on offer. Clinical trials find doctors and patients and convince them to sign up. They thus appear to face similar challenges and may need to install similar processes. Clinical trials are not necessarily akin only to small businesses; some can be viewed as equivalent to quite large businesses with revenues running into millions of pounds and recruitment targets of thousands of participants.

Clinical trials have several stages, including designing the trial, obtaining funding, finding participants, processing results, interpreting the results and reporting the findings. In all stages the key requirement is to 'do good science'. However, in the recruitment stage the most demanding activity is to install and operate a range of effective management techniques, which parallel those for running a successful business. This presents new challenges that require a very different set of competencies to those related to fulfilling the scientific mission of the trial.

### Management and marketing

The modern study of management began with Frederick Winslow Taylor before the First World War.<sup>77</sup> Taylor realised that effective management requires a clear set of values, incisive analytical techniques, evidence-based approaches, and the use of specially devised methods for control and

coordination. For the purposes of this chapter, management is defined as 'getting complex things done efficiently and effectively'. Taylor became known as 'the father of Scientific Management' and many empirical and theoretical contributions since then have taken the study and practice of management forward greatly. Since the 1970s, management has become a legitimate academic study, with most universities offering Master of Business Administration (MBA) degrees and doctoral programmes.

Some, but not all, managers run businesses. A business exists because it finds customers and fulfils their needs, with its costs being lower than the revenue that it receives. A business needs to be entrepreneurial, not least because other businesses compete with it and attempt to capture its customers. There are special management challenges in running businesses<sup>78</sup> that will be elaborated upon later in this chapter.

An aspect of management that has developed markedly over the past 20 years deals with 'big picture' questions such as 'what should we be doing?' and 'what resources will we need?' Questions such as these are answered by senior managers and the field that guides them is known as strategic management. Strategy is constructed as decisions are taken about why the organisation exists (its mission), what it aims to do (vision and goals), its capabilities (core competencies) and its guiding principles (values).

An important speciality within management is marketing, which is the study of what is needed to win and retain customers. Like management, marketing has distinctive frameworks, methods and techniques, many drawn from the social sciences such as sociology and social psychology. Since marketing became better understood in the 1960s<sup>79</sup> it has become ubiquitous with almost every large company, and many not-for-profit organisations, having a director of marketing and a marketing department. The key tasks of a marketing function are to define the characteristics of customer groups (market segments), to devise ways to signal the benefits of

the company's offers (marketing strategies) and to influence the company to meet the needs of the market (be market driven).

Marketing is a set of technologies for finding sufficient numbers of people who want to buy what a company (or not-for-profit organisation) seeks to sell. Clinical trials need people to buy in; hence, for all trials, marketing is fundamental. Trialists cannot avoid being marketers.

A definition of marketing offered by McDonald and Wilson<sup>80</sup> is "a process for defining markets, quantifying the needs of the customer groups (segments) within these markets, determining the value proposition to meet these needs, communicating these value propositions to all those people in the organisation responsible for delivering them and getting their buy-in to their role, playing an appropriate part in delivering these value propositions to the chosen market segments (and) monitoring the value actually delivered". (A value proposition is a bundle of benefits offered that impels a customer to want to buy. For example, the value proposition for a family car may include enhanced safety cots for babies, children's entertainment in the back seats, ample space and stain-proof upholstery. One of these benefits, by itself, will be unlikely to persuade parents to buy. Taken together, the value proposition offered by the motor manufacturer may be sufficient to impel a customer to want to buy.)

McDonald and Wilson's definition concentrates on developing processes that provide an offer that customers consider to be of value. In short, it focuses on the need to have customers pulling the organisation to deliver something that they want. This is the opposite of the conventional view that marketing is about *pushing* products or services that the organisation wants to sell. It can be argued that pushing a product is a sales, not marketing, activity.

An initial survey of the literature on clinical trials shows that the marketing dimension is included tangentially in many trials.<sup>39</sup> For example, trials are generally stated to need recruitment strategies, use of media and data tracking systems. However, the notion of developing and working to achieve a formal marketing plan that covers all of the areas in the McDonald and Wilson<sup>80</sup> definition is absent from all the trial management descriptions examined here.

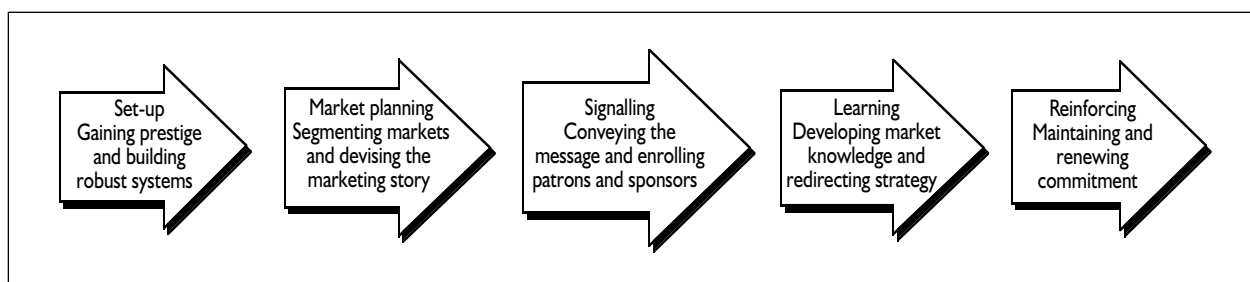
This is not to suggest that clinical trial managers consider the topic of recruitment lightly. Indeed, it

is the dominant preoccupation of many trialists. For example, the Diabetic Retinopathy Awareness Program study<sup>81</sup> undertook many initiatives to recruit volunteers and concluded that "these experiences substantiate the need for a comprehensive coordinated approach, using planned sources, to achieve recruitment success".

When looked at from a business management perspective, it is clear that dimensions of running a successful trial include marketing, sales and ongoing client management. It can be argued that marketing is especially important in clinical trials since, in most cases, those who need to be enrolled to support clinical trials are volunteers who may gain no benefits from participation and can be asked to undertake activities without reward to themselves. Participation in a trial is a formal voluntary act, in that participants need to abide by a set of rules. Accordingly, not only is it necessary for people to volunteer, but they also need to sign up to behave in accordance with a procedure.<sup>82</sup> It has been suggested<sup>83</sup> that "competitive pressures make careful applications of marketing management tools imperative for the survival of time-dependent (i.e. working to time-based targets) non-profit organizations". This point was elaborated in the following observation by the director of investigation services at a contract research company, who observed that "nowadays, recruitment is more complex and so there are increasing requirements around raising awareness with patients".<sup>84</sup>

From a marketing perspective, conducting a successful trial can be seen as a process with five main stages (*Figure 2*). These five subprocesses follow McDonald and Wilson's definition (cited above), but elaborate it significantly. *Table 16* amplifies the purposes and content of each of the stages.

Related to, but distinct from, marketing are sales activities. Selling is a set of activities intended to persuade a potential customer to buy. Selling requires specialised skills, a persuasive case and the capacity to empathise with potential customers. Often selling is a face-to-face activity, but it need not be so. It is possible to sell through the Internet, by telephone, through word-of-mouth, by advertising, and so on. It is considered by some that selling is a base and manipulative activity. Although this can be true, selling is often a mechanism for relating a customer's needs to products or services that are available. Many doctors, for example, spend part of their time selling the benefits of leading a healthier lifestyle.



**FIGURE 2** Five stages in marketing a trial

**TABLE 16** Purposes within the five stages in marketing a trial

| Stage           | Marketing purposes  |
|-----------------|---|
| Set-up          | <ol style="list-style-type: none"> <li>1. To gain the buy-in of the necessary authorities and stakeholders</li> <li>2. To gain the buy-in of opinion leaders whose explicit approval provides legitimacy and prestige for the trial</li> <li>3. To construct a marketing function within the trial and devise robust systems for ensuring that the marketing (and later sales) activities are undertaken efficiently, effectively and in accordance with the values and goals of the trial</li> </ol>                       |
| Market planning | <ol style="list-style-type: none"> <li>1. To identify and describe the distinctive features of the 'segments' of the 'market' to be targeted</li> <li>2. To discover what people in each of the selected market segments value (i.e. what would encourage them to 'sign-up')</li> <li>3. To develop a 'value proposition' (or more than one if required) that can be tested with each of the targeted segments</li> <li>4. To enrol the whole trial organisation in working within the trial's 'marketing brief'</li> </ol> |
| Signalling      | <ol style="list-style-type: none"> <li>1. To convey, fully and persuasively, the 'value proposition' to sufficient numbers of people in the target market</li> <li>2. To convey, fully and persuasively, the 'value proposition' to intermediaries (e.g. doctors or nurses), influencing bodies (e.g. ethics committees) and other agents that can either help or hinder the conduct of the trial</li> </ol>  |
| Learning        | <ol style="list-style-type: none"> <li>1. To learn, through doing, about 'the market'</li> <li>2. To utilise ongoing learning to develop more effective policies and practices</li> <li>3. To evaluate, and redirect the strategy of a trial as learning is acquired</li> </ol>   |
| Reinforcing     | <ol style="list-style-type: none"> <li>1. To maintain momentum by renewing or upgrading 'the offer' made to participants</li> <li>2. To sustain commitment of interested parties and other agencies whose support will be needed</li> </ol>   |

Clinical trials require strategy, management, marketing and sales. Undoubtedly they undertake all of these activities in some way. It is possible, however, that those who define the strategy of a trial, establish its management processes, devise its marketing plan and attempt to sell the benefits of participation may improve their practice by explicitly engaging with the discipline of management. Indeed, Farrell<sup>85</sup> has argued persuasively that it is a lack of solutions to managerial issues that reduces the effectiveness of trials, and Rowe and colleagues<sup>86</sup> suggested that "to get patients into trials more efficiently pharma companies must begin to think like marketers".

Of particular importance is the need to segment the market. This requires identifying and listing the key characteristics of different target

audiences. (It should be noted that a disadvantage of selecting the CRASH trial for the in-depth case study was that for this patient population the aspect of participant engagement could not be explored.) To some extent each will require a distinctive marketing strategy. Market segments vary according to the nature of the trial but, typically, there will be at least five: the potential participants, their relatives, the potential recruiting doctors, senior consultants and nurses (who play a key role in many cases). It may also be necessary to have a marketing strategy for the broader medical community, including opinion leaders who may be crucial to the success of the trial. In addition, it may be necessary to 'sell' the trials to R&D departments and other groups that impact on the feasibility and therefore success of the trial.

## Aims

The aims of Part C were to examine a single trial as if it were a business, to comment on its marketing strategy, and to help the trial team to understand and put in place a marketing plan.

## Methods

One of the researchers in the STEPS team (DF), a marketing specialist from the academic business sector, was invited to work with the MRC CRASH trial. The CRASH trial is a large-scale, placebo-controlled trial on the effect of corticosteroid treatment on death and disability in patients with head injury. The trial aimed to recruit close to 20,000 head-injured patients from hospitals worldwide. Because all of the patients included in the trial were unconscious and thus unable to give informed consent, the relevant MRECs and LRECs had in most cases agreed that the responsible doctor could take the decision to enter a patient into the trial. For this reason the main challenge in conducting the trial was to engage the interest and collaboration of doctors who treat patients with head injury.

DF was given access to all trial related documents (apart from confidential patient outcome data) and interviewed the members of the central trial management team. He visited three participating hospitals in England, observed training sessions and interviewed or facilitated group discussions with doctors (12), nurses (14) and ancillary staff (four).

DF's interview notes were analysed using N-Vivo qualitative analysis software initially, but manual analytical methods were used later as a significant research objective was to highlight what participating agents were not saying, rather than what they were saying. The researcher invited a professor of management to check his interpretative framework against the raw data. He presented his findings to the STEPS research team and also to researchers at the Centre for Research in Innovation Management. Exposing an emerging conceptual model to experienced academic researchers, trialists and trial managers provided an opportunity to validate the researcher's constructs and extended the theory building process.

Using grounded theory<sup>87</sup> a reference model was developed that could be used to assess the sales and marketing capability of the trial. A one-day

marketing workshop using an action research approach was held with the trial team to provide insights into the extent to which concepts and practices from the business world might have relevance to management of clinical trials. Early in 2004 an additional 5-hour workshop was held with representatives from five trials (one of which was the CRASH trial) to gain further insight into the heuristic value of the reference model.

Processes for testing the reference model, using an action research method, with the full-time staff conducting the CRASH trial provided additional, although case-specific, data. For example, a one-day workshop was held on the strategy of the CRASH trial.

In the trial documentation (a form of business plan) it was stated that the aims of the trial were to deliver a certain number of cases by a certain time. In the workshop this statement of goals was elaborated and it was agreed that the mission of the CRASH team was "to answer an important scientific question thereby providing clinicians with evidence-based knowledge that will help them to treat head injury patients better by:

- efficiently and effectively conducting the world's largest head injury study;
- recruiting and following up 20,000 patients by 2006;
- ensuring that the evidence collected and conclusions drawn meet the highest standards of medical and scientific practice."

At the same workshop, eight core values were agreed upon:

1. We maintain the highest ethical standards: maintaining confidentiality and abiding by the best medical practice.
2. We ensure that data are reliable, valid and verifiable.
3. We build quality into every activity and into our system as a whole: 'quality before quantity'.
4. We are unique, innovative and original: seeking new ideas and using them to benefit the trial.
5. We are efficient (fast, cost-effective and error free).
6. We are a collaborative organisation: serving the needs of all partners and stakeholders.
7. We communicate effectively, openly and fully.
8. We are people-orientated: personal and caring.

The mission and core values elaborated the goals of the CRASH trial, humanised its tasks and defined ground-rules or collective norms. From



this and other action research interventions it proved possible to assess how a trial management group responded to interventions more commonly used in commercial organisations.

## Results

The researchers considered that it would be impossible to audit the managerial effectiveness of a trial without templates of what a well-managed trial was like. Accordingly, the results presented in this section are models, not findings. Later research can test the models and use them as audit tools.

Two models will be presented. The first is systemic, dealing with the management issues for a trial as a whole. The second, and more detailed, model examines marketing and sales issues for clinical trials, since these were the areas studied intensively in the CRASH study.

### A tentative systemic model

Since the 1970s, management studies have emphasised that organisations need to be seen as systems with interacting activities.<sup>88</sup> The performance of the system as a whole depends, at least in part, on the appropriateness of the activities to the performance of the system as a whole, the efficiency by which the activities are performed and, crucially, how the activities relate together to form a gestalt, or whole.<sup>89</sup> An example illustrates the point. In a busy primary care practice it may be that the clinical activities could be conducted efficiently as there are sufficient numbers of trained doctors available. However, if systems for scheduling the doctors' workloads are slow and prone to error the performance of the practice as a system will be degraded.

A clinical trial requires a sequence of activities to be completed. Within each activity category many specific activities generally take place. In management jargon this is known as a value chain, since each of the activities should create value (i.e. provide benefits for one or more of the stakeholders). The activities listed in a value chain diagram are very broad in scope, for example, 'operations' would be regarded as 'an activity'. (In management jargon, 'operations' means the work needed to turn raw materials into finished products. In a factory, 'operations' is the work that needs to be done, for example, to turn planks of wood into furniture; in an insurance office 'operations' includes work that needs to be done to turn an enquiry into a proposal. In a hospital,

'operations' is the work that needs to be done to care for patients.) Accordingly, the effectiveness of the trial is a consequence of the degree to which each set of activities is appropriate and performed well, and the activities are integrated together.<sup>90</sup> Some activities are core, in that they directly support trial effectiveness. Other activities are support, in that they are necessary but do not directly add value to trial performance.

The researchers were unable to find a systemic or value chain model of a clinical trial in the literature and so to understand better the specific management issues of a trial a speculative value chain model was developed (*Figure 3*). The arrow layout is the conventional format used in management analysis. This diagram shows the relationship between the key sets of activities that deliver value to clinical knowledge. There are six core activities, shown in the centre of the arrow diagram, and four non-core activities that enable the core activities to be performed. The core activities are likely to be understood, but the value added by non-core activities is less obvious. This study found that it was vital for a trial to win support from the multiple stakeholders, have strong norms and processes for undertaking 'good science', be able to manage all of the soft and hard activities involved in managing a complex project and, lastly, to ensure that funds were spent well and that expenditure was tracked.

The extent to which a trial delivers its promise will be determined by the efficiency and effectiveness by which the ten activities of the value chain are performed and the degree of integration between them. It is to be expected that the construction of a value chain for a clinical trial will differ to some extent according to its specific requirements. It is emphasised that sales and marketing are limited management activities. Simply getting sales and marketing right will not be sufficient.

Workshops held with the CRASH trial team found that there was a need to upgrade systemic thinking. Each person working on the trial had their area of responsibility, but issues that crossed organisational boundaries were discussed less and were identified as problematic. Each activity in the value chain presented a distinct management challenge. For example, in the CRASH trial many participating hospitals were overseas and there was a need to travel extensively to gain stakeholder support and use web-based communication methods to maintain communication and commitment.

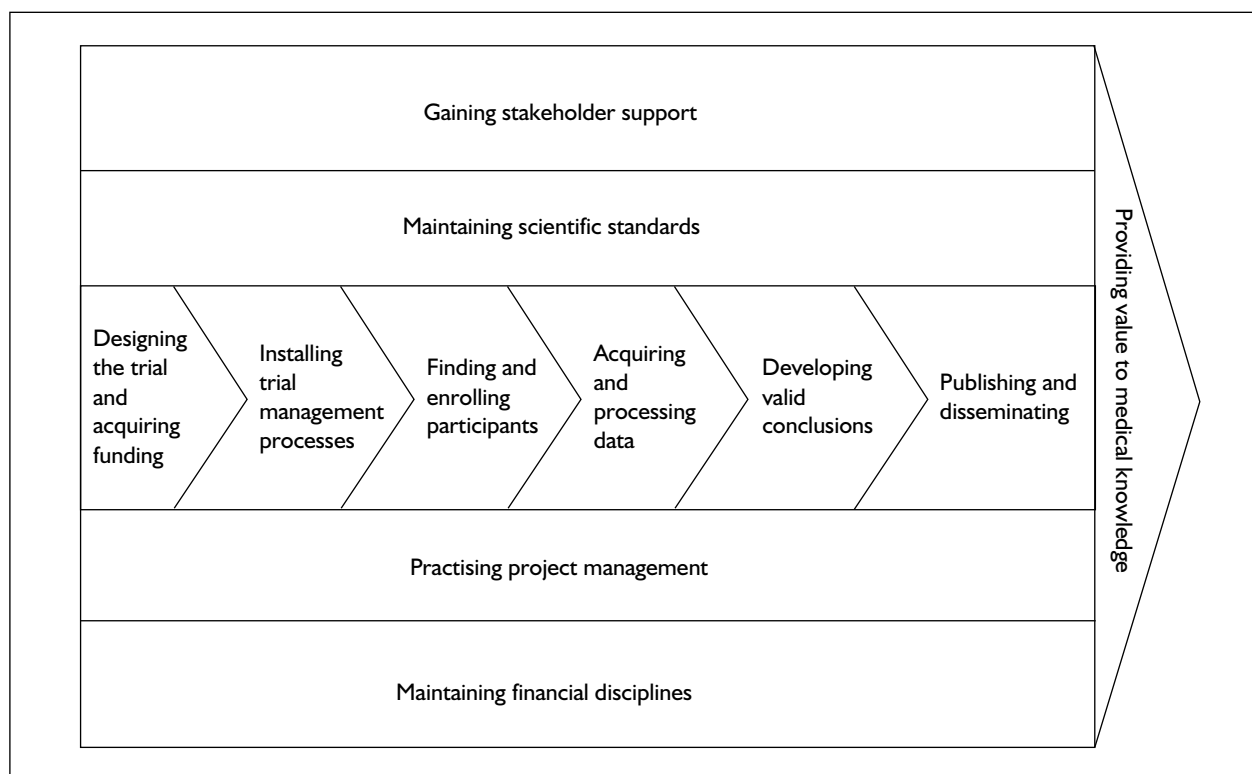


FIGURE 3 Value chain model

### A marketing and sales reference model for trials

The marketing challenge facing the CRASH trial team is different to that of a company that is selling soap or offering package holidays. When companies sell a product they attempt to convince a potential customer that they will gain benefits directly from their purchase. In CRASH the trial managers were seeking to gain a commitment to engage from clinical professionals who would make no material gain for themselves.

Accordingly, the CRASH trial was selling an opportunity for clinical professionals to participate in improving future clinical practice, an activity that can be seen as being akin to a charitable endeavour.<sup>82</sup> A challenge for the CRASH trial was to sell the notion that if a clinician signed up to the trial then medicine itself would progress and the clinician would be fulfilling a professional obligation.

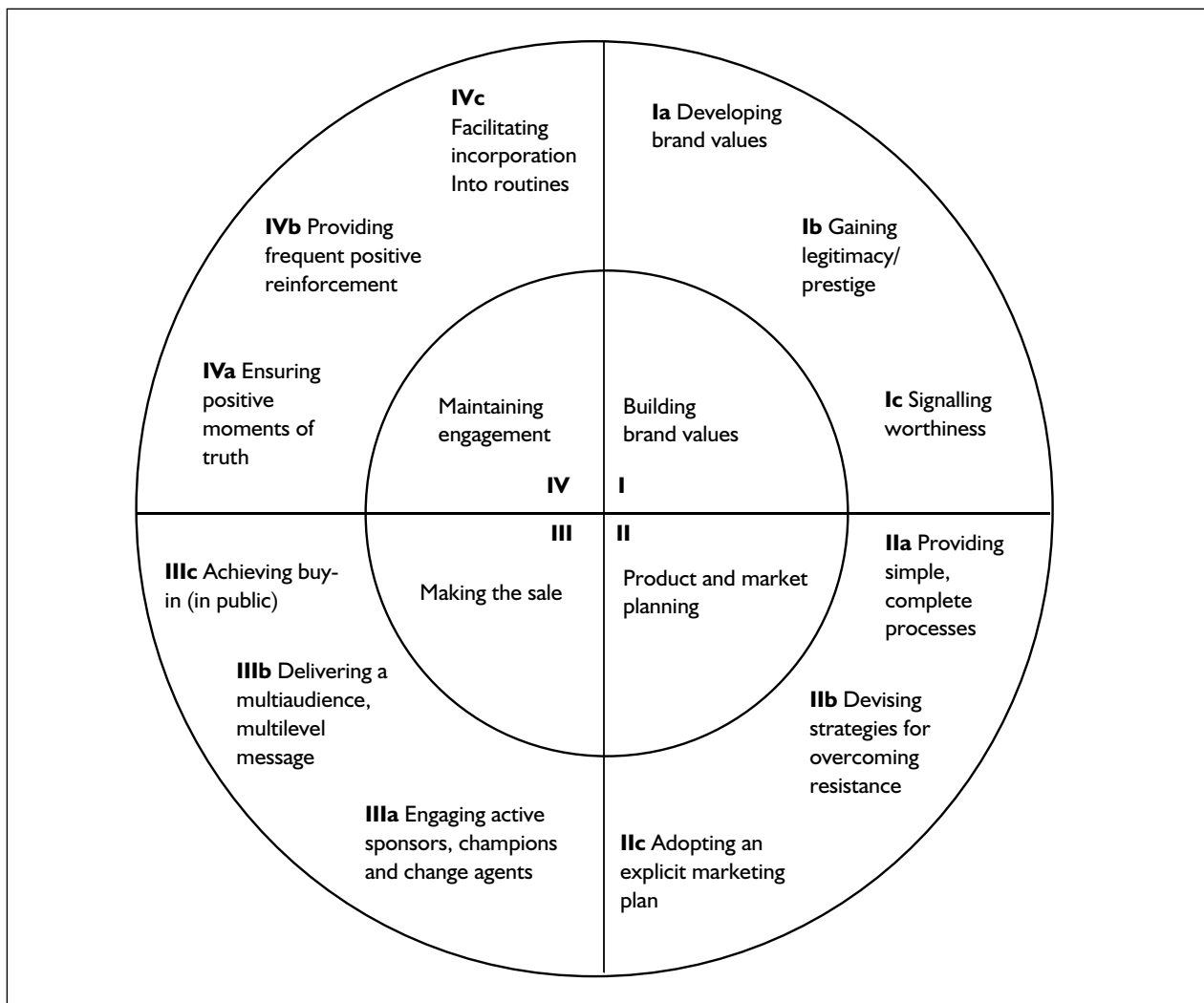
The complex nature of the sale [of a trial that requires the participation of staff in accident and emergency (A&E) departments] is illustrated by the comments in *Box 5*.

Another dimension of the marketing challenge was found to be the difficulty in understanding the reasons why participants (in this case hospitals) signed up and what motivated them to fulfil a

- Enrolment happens by word of mouth. Friends talk to friends
- I need to opt in both in principle and then you have to remember it when a patient is in front of you
- When someone keen leaves then it can fade out immediately
- So many things are happening at the same time that it is difficult to think about the trial
- It can happen in the middle of the night. The people on duty need to remember that this patient is suitable for the trial
- It needs someone to be assertive – there's a lot going on
- It feels like an optional extra
- A reluctant person can mean 'no'
- Some A&E departments are just not organised enough to do anything extra
- Less badly injured patients may be in a side room, so we just don't think about them for the trial

BOX 5 The complex nature of the 'sale'

commitment that had no sanctions for non-performance.<sup>91</sup> An analysis of feedback from participating hospitals concluded that they opted in for a variety of reasons, including the perceived merits of the study, the efficacy of the sponsors and advocates, the status provided to participants through participation and the affordability of participation (see section IIa of *Figure 4*).



**FIGURE 4** Reference model

It became clear that the CRASH trial team was not ignorant of the basic principles of sales and marketing. Many of the attitudes, concepts and practices of modern marketing had already been adopted. Indeed, the trial manager made the comment in an early interview that “it’s all about selling”. However, the trial team was unaware that they were using, at least in part, a distinctive conceptual framework developed in the business world; to them it was common sense. Perhaps because the CRASH team’s marketing approach was self-invented, some practices were state of the art, whereas others were weak or absent.

Working with the CRASH trial team, DF sought to answer the question, ‘if this was a business, then what policies, practices and capabilities would be needed for the marketing challenges to be met?’ A reference model was developed to define the capabilities required for each of these stages (Figure 4) that offered a systemic ideal type, that

the trial could use to define excellence.<sup>92</sup> The model has four domains and 12 components and is illustrated as a wheel diagram. The components and their relevance to the CRASH trial are outlined below.

The wheel diagram could be used as the framework for an auditing tool. The management team conducting the CRASH trial assessed the components’ effectiveness and efficiency in relation to each of the 12 components and illustrated these as a spider chart on the diagram. Since all of the components are important, it was assumed that higher scoring components represent strengths that should be amplified<sup>93</sup> and lower scoring components are blockages to be reduced or eliminated.<sup>94</sup>

The 12 components are described below, with comments on performance of the CRASH trial related to each dimension.

### **1a. Developing brand values**

Brand values define what a brand is and what it is not; that is, its personality. A clinical trial can be seen as a brand. Without explicit brand values it is impossible to communicate a coherent and persuasive perception of a trial's promise: what the trial intends to deliver to medicine, doctors, patients, and so on. CRASH had developed strong brand values, including scientific rigour, inclusiveness, simplicity and high levels of feedback to participants.

### **1b. Gaining legitimacy and prestige**

Trials need legitimacy: they need to be positively tagged by association with prestigious individuals and institutions (so a hospital doctor may say, "I know that this is an important trial because Professor X, whom I know and respect, is supporting it"). Legitimacy and prestige provide persuasive credibility, which is key to gaining access to decision-makers. CRASH benefited greatly from the public support of leading authorities, notably the MRC, the CTSU at the University of Oxford and respected academics. However, an assessment of the extent to which the CRASH trial had acquired a full portfolio of legitimatising agents identified that one important speciality (neurosurgeons) had never been won over, and disadvantaged the trial's persuasive credibility. This legitimacy gap is now being addressed.

### **1c. Signalling worthiness**

It is vital to signal to likely participants that this trial will create greater value than the costs (time, effort or money) involved. Buy-in is more likely to occur when participants realise, and identify with, the potential benefits that will be delivered by the success of the trial. CRASH made great efforts to signal its worthiness, especially through presentations at conferences, journal publications, advertising, public relations and training materials. Anecdotally, it was considered that these signalling activities had been successful, but no procedures were in place to gather data systematically on the extent to which the trial had achieved an adequate share of voice (i.e. the trial was known to potential participants).

### **1la. Providing simple, complete processes**

Trials require participants to undertake additional work. Providing simple, complete processes reduces the costs of participation and increases the chances that involvement will be affordable. CRASH had developed streamlined processes that were piloted and improved frequently. However, some difficulties remained. For example, trial

Nurses' comments included:

- Nurses are notoriously resistant to trials: they seem less than human
- Nurses see themselves as advocates for the patient
- Numbers are not interesting to nurses
- We don't want research. We want to give the best treatment NOW
- There's generally a boss nurse and what s/he says goes

Doctors' comments included:

- What's special about this trial?
- Will it involve much work?
- Do I believe in this? Is it right?
- I need my questions to be answered, before I can commit myself
- One of the problems is to enrol the bigger team, especially with transfers (i.e. patients that are sent to other hospitals for further treatment)
- What are likely to be the long-term benefits?
- What's in it for me?
- Some little things can be difficult – finding the patient's phone number, for example. It can put you off doing it again

### **BOX 6 Potential participants' objections**

treatment packs for overseas participants are often held by overseas customs, requiring considerable effort from trial collaborators to release them. Also, filling in data forms and sending them to the trial office could involve substantial work. Although the trial team developed better methods for data collection, they were not in place at the start of the trial. During 2003 processes were simplified further with improved online input.

### **1lb. Devising strategies for overcoming resistance**

Potential participants frequently raise objections (*Box 6*). It is likely that other trials will have different perceptions and resistances. An effective marketing plan will deal with the existential reality of each of the targeted groups, not bundle them together into a generalised marketing/sales plan. Trials should have standard and persuasive answers to these. Having a persuasive answer for each objection increases the probability of making a sale. CRASH has a list of answers to frequently asked questions, but the team could do more to deal with unspecific resistance, for example, potential participants saying "it's a good trial but we just don't have the time". Again, work is underway to improve the capacity of the trial staff to provide accurate, speedy and persuasive answers to objections.

### **1lc. Adopting an explicit marketing plan**

The marketing of a trial is too important and too complicated to be done informally. A formal

marketing plan is required that should include a definition of target market segments (groups that need to buy in to the trial) and the trial's unique selling points. It is to be expected that the marketing plan will need to be revised frequently, probably every quarter. CRASH did not have a written marketing plan until this study was undertaken. The trial team had already appreciated that a major market for the trial comprised hospitals in countries that had high rates of head injuries, and identified nine segments: opinion leaders (national/international) in neurosurgeons, intensivists, A&E specialists, A&E nurses, hospital administrators, registrars, ethics committees, government health departments and drug manufacturers. Each of these segments needed a distinctive marketing and sales plan.

A formal marketing plan identified the need for additional resources to be allocated to winning participation from such hospitals. The CRASH team later identified five levels of commitment to the project by potential participants and defined strategies for each. The levels and strategies were: (1) the uninformed (inform and persuade with targeted stories); (2) the unconvinced (address concerns point-by-point; get to yes); (3) the laggards (enrol, cajole, facilitate and target); (4) the steady performers (reward, renew, upgrade and recognise); and (5) the stars (honour, learn from, exploit and nourish).

### **IIIa. Engaging active sponsors, champions and change agents**

Selling a trial to prospective participants requires persuasion. This requires enrolling sponsors (public advocates), champions (activists) and change agents (facilitators). Trial managers need a network of supporters to spread the message. Persuasion is more likely to occur if the advocate is respected and known personally to the prospective participant. CRASH had enrolled sponsors and sought to encourage champions. However, performance was patchy. Increased recognition of the importance of this activity has meant that the CRASH team is now making systematic efforts to develop stronger networks of direct influence.

### **IIIb. Delivering a multiaudience, multilevel message**

Trials need to convey sales messages through publicity, presentations, training materials, and so on. These should be tuned to the distinctive needs of target groups; for example, surgeons are likely to be persuaded by different messages to administrators or nursing staff. Speaking in the language of the person being targeted and

addressing their particular pattern of motivation is more likely to succeed than a one size fits all approach. CRASH had gone some way to developing distinctive ways to communicate with its intended audiences, but this was insufficient and the communication was generic, not segmented. Currently, work is underway to refine further the communication strategy using the notion of micromarketing (i.e. tuning messages to the specific needs of market segments).

### **IIIc. Achieving buy-in (in public)**

Public buy-in requires that intended participants announce their commitment to join the trial in a setting where they are heard by others. This is important because when someone states, in public, that they are willing to undertake an action, then they are much more likely to abide by their commitment than if they take a silent decision, which can be forgotten easily. CRASH has achieved a measure of encouraging and reinforcing buy-in, for example by naming new participants in its regular newsletter. However, more can be done and strategies are being developed to achieve more complete and memorable buy-in moments.

### **IVa. Ensuring positive moments of truth**

People evaluate organisations (including trial management teams) on the basis of their experiences at moments of truth. For example, if a doctor has a technical question about entering a patient into a trial he or she will gain a strong impression of the trial management team's competence by the way in which the query is handled. If an organisation behaves well in a moment of truth then loyalty grows; if not, loyalty diminishes. A core value of the CRASH trial was to be user-friendly and this meant that the trial team tried to be helpful on all occasions. However, potential moments of truth had not been identified systematically and work is underway to understand better the key moments when participants come to define the CRASH trial; for good or ill. Once this assessment has been completed it will be possible to improve the way in which moments of truth are handled.

### **IVb. Providing frequent positive reinforcement**

Positive reinforcement for existing participants should be an important part of a trial's participant retention strategy. It is more expensive to recruit new participants than to retain existing participants. CRASH had gone some way towards recognising and rewarding participants, but its strategy was to honour the highest yielding hospitals, which could be a disincentive to those

whose contribution to the trial was more modest. In 2003, the policy was changed so as to give positive reinforcement to all contributors.

#### **IVc. Facilitating incorporation into routines**

Activities that become embedded as routines are more likely to be done than one-offs. Trial procedures should be incorporated into the routines of units undertaking the work. CRASH had incorporated this principle into the development of its training materials, but did not emphasise it. More can be done to embed CRASH as a standard operating procedure in hospitals, and this is being addressed.

## **Discussion**

### **Statement of principal findings**

Farrell, among others, has been arguing for a greater recognition of the role of management in the conduct of clinical trials,<sup>85</sup> but without spelling out what this means in detail. This study has found that it is possible to construct useful reference models that assess the managerial capability of a trial, both as a totality and in relation to marketing and sales activities.

### **Strengths and weaknesses of the study**

The key strength of this study is that, to the authors' knowledge, for the first time in academic literature, it provides two models that give a conceptual architecture that provides an opportunity for trial managers to review their strategic, managerial and/or marketing strengths and weaknesses.<sup>95</sup>

The weaknesses of this study are that it was based on a single case, that tests to prove the validity of the models were rudimentary, and it has not been possible to compare trials that use the reference model approach with trials that do not use it.

Although the researchers consider that there are considerable benefits in reflecting on trials from a business perspective, it is important to emphasise that they are not businesses. Management and marketing provide frameworks and tools that can improve the probability that a trial will achieve its scientific goals. However, it would be damaging if an interest in developing trials as 'businesses' led to separation of the scientific aspects and trial management processes. As mentioned above (see the section 'Management and marketing', p. 49), participation in a trial generally brings no direct benefit to either clinical teams or participants, as the likely beneficiaries will be future patients. It is

important to recognise that there are substantial differences as well as similarities between trials and most forms of business. Techniques of management and marketing should not be adopted uncritically, but they can provide a valuable input into the emerging theory of trial management practice.

The reference models described above should be seen as tentative frameworks rather than definitive templates. They were developed from a theory-building process from a single trial and are best considered as a set of provocative hypotheses; later they may be developed as provisional audit tools. As indicated above, an audit of the CRASH trial enabled components that were considered to be weaker than others to be identified and initiatives undertaken to improve in these areas.

### **A clash of cultures?**

Medicine has a basis in scientific method, of which RCTs are a prime example. Management is fundamentally different as it is rooted in practice and can be considered to be a craft in the medieval sense of the word. "Mastery requires a combination of science, art, practical experience and learning from accomplished masters."<sup>96</sup> This is not a hard and fast distinction, as much clinical practice is craft based, and some management tasks (e.g. the statistical analysis of product quality problems) draw from scientific techniques and are evidence based.

Henry Mintzberg described the essence of management when he wrote:<sup>97</sup>

Science is about the development of systematic knowledge through research. That is hardly the purpose of management. Management is not even an applied science: for that is still a science.

Management certainly applies science: managers have to use all of the knowledge that they can get, from the sciences and elsewhere. But management is more art . . . .

The art of management lies, in part, in the ability of the manager to respond to the chaotic nature of the real world.<sup>89</sup> The different bases of knowledge on which medicine and management rest may present difficulties to scientists who seek experimental evidence and tend to eschew a discipline that is based on craft principles.

However, clinical trials are not just medical activities; they are time-bound businesses that have two interdependent sets of processes, one clinical and the other managerial. In the main, since trials are seen as clinical endeavours, they are dominated by clinical issues and led by people

with clinical skills. This is essential for certain policies and practices, but this cultural bias can result in the managerial aspects of trials being relatively neglected. If this is true, even if only in part, it means that the radical improvement of clinical trials could require different ways of defining the challenges of running successful trials; in particular, to ensure that they are seen as management challenges that can benefit from the informed use of selected management processes and techniques.

These considerations suggest that looking within past trials for the answers to the problem of underperforming trials is necessary but will not be sufficient. In order to improve trials it will be necessary to look outside the world of clinical practice, into the worlds of business strategy, management, marketing and sales, to gain a fuller understanding of what can be done to upgrade the performance of clinical trials. This insight is not new. Donovan and colleagues<sup>98</sup> state that the “methodological literature (on trials) is almost exclusively statistical and epidemiological, and very little of it is concerned with the conduct or the particular demands that trials put on trialists and participants”.

### **Meaning of the study: possible mechanisms and implications for clinicians or policy makers**

This study could begin to change the ways in which trial managers undertake their work. It also provides a new and different way to think about the skill sets needed by those who manage clinical trials. In essence, the message of this study is simple, even simplistic. It is that trials are both complex projects and businesses (they need to find customers). The key implication for clinicians is that insufficient attention to management issues and marketing or sales activities will degrade the performance of the trial.

There are significant implications for policy makers and funding bodies as well. If the tentative conclusions of this study are correct, then the funders will need to examine more than the scientific case before sponsoring a trial. They will need to see a business plan, be assured that all of the required elements of the business system will be developed and have a marketing/sales plan. Since a successful trial requires both good science and good management, both need to be given their due weight.

Trials need participants just as companies need customers. Trials have something to sell, perhaps a

promise that, at some time in the future, other sick people will benefit from the research being undertaken. Trials target participants, develop a story to describe their unique selling points and attempt to persuade people to buy in. Once a trial has enrolled a participant it seeks to retain him or her. In these and many other respects trials are, in fact, businesses.

But there are differences. Business is about profit. Medicine is driven by human values. It would be wrong to suggest that trials need to be more like businesses; rather, it is suggested that trials may benefit from using business concepts and business techniques.

There is a potential benefit for using the reference models in other trials, especially early in their life cycle; this can be described as speeding the learning curve. It took many months of management effort for the CRASH trial team to develop their approach to marketing the trial. The clinical coordinator considered that if they had had access to an appropriate model at the beginning it would have accelerated its development and reduced costs, enabling more effort to be invested in trial activities.

The world of business has spent more time and a lot more money than health management in finding tools for marketing and selling. In the authors' opinion, it makes sense for trialists to learn from business where this could improve trial performance.

### **Unanswered questions and future research**

There are five unanswered questions that the authors consider to be worthy of further research. These are:

- Are the reference models outlined in this chapter complete and correct for other trials?
- How can useful audit tools be developed from the reference models?
- What competencies do trial managers need to manage the business dimensions of their trial?
- How can third parties such as advisers, assessors or sponsors intervene successfully in a trial in order to improve its performance as a business?
- What should funding bodies ask about the proposed business model, management system and marketing/sales of a trial requesting funding?

If there is sufficient commitment to improving the business management of trials then the reference

models outlined above will need to be considered in the context of other trials to assess their validity. In addition, recognition of concepts common to more than one trial does not necessarily imply that their inclusion into a strategy for future trials will increase recruitment. This strategy needs to be tested empirically. However, the perspectives given by this study have proved provocative and have stimulated much consideration into what it means for a trial to be well managed.

If this does not happen, then Farrell's call<sup>85</sup> to address the role of management in the effective delivery of a trial will have fallen on deaf ears and some trials will continue to disappoint, despite their scientific merit. Nevertheless, it is important to emphasise that ethics must not be compromised and that improved management and marketing effectiveness must not be allowed to become unethical, thereby causing distress to patients and their families or to healthcare workers by using a hard sell inappropriately.

### **Personal reflection**

Although some trialists tend to denigrate forms of knowledge other than that from the hard sciences

(which can be a barrier to cross-disciplinary learning), the management researcher (DF) found himself at home in the trials world since the sorts of issues that trial managers raised were variants of those that occupy managers in the commercial world. He felt that the groups that he encountered had remarkable energy, commitment and sense of mission, and he saw that the management policies and practices that he introduced using an action research approach were not alien: they were developments of approaches that were already being used by the trial management team.

As academic researchers we surround our findings with caveats, but managers from the world of business can be cavalier and say, "yes, a trial is a business and a trial needs to employ up-to-date management practices if it is to achieve its promise; simply looking within the world of trials will not provide all the answers. It is time for trial managers to take as much pride in the management of their trial as they do in the medical advance that it delivers".



# Chapter 5

## Discussion

This chapter first refers back to the commissioning brief and the successful application from the STEPS team. It then briefly summarises the main findings from Parts A, B and C, and their individual strengths and weaknesses. Finally, the authors consider what has been learnt from the study overall and what questions remain unanswered, and suggest areas for future research.

### Background

The commissioning brief for this project followed from the perspective that although large sums of money are spent on multicentre trials, the trials often fail to achieve planned levels of recruitment. Fast recruitment is desirable as it brings important benefits in terms of providing knowledge more quickly and reducing research costs. It is possible that differences in the design and execution of these trials could result in better or worse recruitment rates. The HTA Programme and MRC therefore jointly prioritised this research to “learn lessons latent in the existing experience” of such trials.

The STEPS team adopted both quantitative and qualitative methods to concentrate on factors that may affect participation of clinicians and collaborating researchers (rather than patients) through three components: an epidemiological review of a cohort of multicentre trials funded by the MRC and the HTA Programme; case studies of four trials that appeared to have particularly interesting lessons for recruitment; and a single, in-depth case study to assess the feasibility of applying business theory to trial recruitment.

### Principal findings, strengths and weaknesses

#### Part A: epidemiological review

The results of the epidemiological review of MRC and HTA Programme multicentre trials confirm the concern expressed in the commissioning brief that failures to achieve projected targets for participant recruitment, extensions of the recruitment period and supplementary grants are indeed common.

As few as one-third of trials recruited to 100% of original target and around one-third had extensions. The analyses within this cohort of factors associated with successful recruitment (from the research literature) provide some support that the intervention only being available inside the trial, having a dedicated trial manager and being a cancer trial or a drug trial were associated with success. However, these findings should be interpreted cautiously; the confidence intervals were all wide, at best these associations were only marginally statistically significant and the trend for some other factors was towards a negative association.

The strengths and weaknesses are discussed in Chapter 2. The main strength was that it included a systematically identified, complete cohort of trials from a wide spectrum of clinical areas, clinical settings and geographical centres. The data were prospectively collected for other purposes and so were unlikely to be biased in respect to the questions being addressed for STEPS. An important limitation was the number of trials available for analysis. Although an attempt was made to include as many studies as possible, there were fewer than had originally been anticipated and a sample size of 114 gave only limited scope for exploratory analyses. As in the commissioning brief, the planned level of recruitment was used as a surrogate measure for the ‘success’ of a trial. As indicated in Chapter 2, the use of this marker as a sole indicator of recruitment success is rather limited, as initial sample size estimates are often more an informed guide, based on imperfect information and other considerations such as feasibility and cost. Arguably more significant measures, such as the extent to which the trial question has been successfully addressed, the perception of funders and other key stakeholders as to whether the trial was successful, and the impact of the results on clinical practice, would be more useful. Other necessary limitations of the epidemiological approach, such as the secondary use of data collected for other purposes (including the misspecification of the ‘exposure’ variables, and variation in the quality of the reporting), and interrelationships between possible explanatory factors, mean that conclusions about causative

factors must be tentative. Although there were some attempts to go back to PIs for further details and understanding, these were limited in scope owing to restrictions in the STEPS budget.

This component proved less useful than expected for exploring factors related to recruitment. No trial was identified that showed a clear change in the recruitment rate at a particular point in time. Hence, although a range of strategies aimed at improving recruitment was described (*Table 13*), it was not possible to assess the extent to which they were causally linked to changes in recruitment. The value of this part of the study was therefore primarily as a descriptor of the problems and of trialists' attempts to overcome them, rather than providing evidence about how useful the strategies were.

### **Part B: case studies**

The results of the in-depth analyses of interviews from four trials considered by their funders to be 'exemplars' suggested that successful trials were those addressing clinically important questions at a timely point. The interviewees highlighted that the trials were led by investigators who were held in high esteem by the interviewees, and they were firmly grounded in existing clinical practices, both so that the trial processes were not alien to the clinical collaborators and so that the results could be easily applicable to future practice. The interviewees considered that the needs of the patients were well served by participation in the trial. Good groundwork and excellent communication across the many levels of the complex structures of trials were considered to be extremely important, including training components for learning about the trial interventions and processes, as well as team building. Clinical collaborators particularly appreciated the clear delineation of roles which released them from much of the workload potentially associated with trial participation. Although the perception of 'success' was not in terms of the study results (as only HPS had reported its findings), there was a strong feeling from the interviewees that they were proud to be part of a successful team, and that this pride in itself fed into further success.

The main strength of Part B was that the in-depth investigation into the four trials took an independent outsider perspective. By building on the experience of Part A, the focus shifted from a restricted definition of success as meeting the recruitment target within the planned time-frame to funders' perceptions of successful trials. The

four trials were all aiming to be the largest of their kind in the world, and spanned a range of clinical and research situations. They were not chosen as 'easy' trials. Indeed, all had faced recruitment problems, and extra insights into the working of trials were afforded by the descriptions of these problems, and strategies invoked to address them. The 45 interviewees performed a range of roles within the trials. Enabling them to reflect within semi-structured interviews allowed them to consider their trials as a whole, not merely in terms of meeting recruitment targets, and their emphasis on the necessary foundations for building a trial is a facet that does not appear to have been previously reported.

The main weaknesses of Part B have been mentioned in Chapter 3. Only four trials were involved, and this is not merely a small number, but possibly atypical of successful trials. The interviews were with people intimately involved with the trials and therefore did not include the perspectives of people with more peripheral roles, such as DMCs and TSCs. No interviews were conducted with teams within trials that were not exemplars. These limitations were mainly due to delays from the RECs and trust R&Ds, and to restrictions in the STEPS period and budget. The implications are that it is not known to what extent the perceptions of those involved in these exemplars differed from those in other trials that were less successful. Most, if not all, PIs are likely to argue that their own trials are important and timely. The other features identified that are common to all four exemplars, such as the importance of good communications, are likely to be essential for successful trials, but would not by themselves guarantee success. It was planned to extend this component of the project to address these issues if further funding had been available, but this funding was not forthcoming.

### **Part C: the clinical trial as a business**

The main result of Part C was to draw attention to a body of research and practice in a different discipline (academic business studies), and generate a reference model derived from a combination of business theory and work within the CRASH trial.

Part C complements the emphasis on trial processes in Parts A and B. Disciplines often work on their own, and an important strength of Part C has been to make explicit connections between the management of trials and the management of

businesses. In the CRASH trial, this enabled identification of weaker managerial components and initiatives to strengthen them.

The main weaknesses of Part C have been mentioned in Chapter 4. As with Part B, it is based on a case-study approach, and the CRASH trial may be a different case in important ways from other trials. For example, the CRASH trial involved patients who were unconscious and hence recruitment focused on the participation of clinicians. In contrast, in most trials, efforts are concentrated on recruitment of patients. In addition, the management approach has not been formally evaluated even within business settings, and it is not clear whether the initiatives that follow from developing and applying the reference model will be effective in increasing recruitment or other aspects of the success of CRASH or other trials.

Nevertheless, the authors see the outputs of this component as potentially the most useful for addressing the commissioning brief. The reference model developed for the CRASH trial could provide a template, with the potential for those managing other trials to use or adapt it, especially at the foundation stages. Parallels can be drawn with professional behaviour change research where psychological models are being used to address the reasons for unwanted behaviours and hence to design appropriate strategies for behaviour change.<sup>99</sup> The reference model derived from this project could be used as a diagnostic tool if a trial has difficulties and hence as a basis for deciding what type of remedial action to take. It might also be useful for audit of a trial's progress, such as during external review.

## Discussion of the overall findings from STEPS

Initially, trials that had recruited to their target sample sizes were considered as successful, and Part A has clearly confirmed there is a problem in terms of trials not reaching their targets within the specified time-frame and budget. This therefore seemed a sensible starting point given that rigorous scientific peer review had agreed what sample sizes were appropriate, and recruitment is a key element for trials, and it may be a *sine qua non* for a successful trial. None of the STEPS components was, however, able to provide definitive answers about what exactly are the causes of or the solutions

to the problem of not achieving recruitment targets.

Rather, the research has pointed to some of the complexities in trials and cast light on the question by asking: 'what makes a trial a success?' It was concluded that recruitment is only one aspect of success and what matters is whether the trial has provided answers to important questions. 'Important' may have a number of dimensions in the context of trials funded by the MRC and HTA Programme. For instance, will it have a beneficial effect on patient care, either directly or indirectly? Does the trial address major public health issues for large numbers of people (as in HPS), or does it help to clarify end-of-life decisions for a small number of cancer sufferers (as in FOCUS)? Does it add pieces to the jigsaw of cancer care, or is it cutting-edge science? Does it help to reach patients who are hard to bring in to trials (as in ELEVATE and TOUNCAN), and perhaps set up networks of clinicians prepared to take part in future trials?

Importance from the standpoint of Part B cannot just be about finding positive answers, as only one of the four trials (HPS) had reported results. With the help of the HTA Programme and the MRC, four exemplar trials were identified. In the interviews for Part B, participants appeared to agree that they were examples of successful trials. They exuded a feeling of confidence in their teams and shared enthusiasm about their trials. Perhaps their self-belief was infectious and helped them in 'marketing their trials to their collaborators and to their funders'.

These four trials were not unusual in returning to funders for extensions: based on the findings from Part A, this applies to around 50% of all trials, most of which were awarded extra funding. It is unclear whether this is because the trials are underfunded in the first place, because applicants are not able to predict the funding that will be required, or because circumstances change between the time of the application and the recruitment phase of the trial, or because investigators are strategically underbidding to get a foot in the door to obtain some funding, even if this is unlikely to be sufficient. Even though large sums are spent by the MRC and HTA Programme on trials (although the amount is small in relation to the overall budget for the NHS), there is a strong perception from trialists that money for publicly funded trials is tight. Additional sources of money were sought in three of the four Part B trials. Although much of this was from the

pharmaceutical industry, many of the trials in the MRC and HTA Programme portfolio are for research that industry is not interested in funding. Dual funding brought concerns about clinical and academic independence, and the effort to obtain the additional funding represented an important drain on the time and energies of the investigators.

STEPS suggested that the science and budget at the application stage need to be complemented by different capabilities for setting up and running trials. Particularly in trials that may be underfunded, the techniques of social marketing (as used for charities), building on shared values, may be helpful in motivating collaborators to participate. Similarly, funders are mainly experts in the scientific domains, but may be less skilled in assessing the strength or weaknesses of the trial processes.

### Provisos

It should be noted that STEPS was based on MRC and HTA Programme-funded trials. The conclusions may therefore not generalise to other funders of trials (e.g. charities and industry), although some of the trials in both Parts A and B had dual funders. In addition, the study was conducted at a particular point in time, and the findings may become less relevant for future trials.

## The research process

### Multilensing

STEPS has used three different approaches to investigate aspects of the same perceived problem of poor recruitment in trials. At one level, these approaches could be seen as setting down three different roads that do not meet each other. In practice, although some individuals were more involved in one part than another, the three parts have all been influenced by the different perspectives of all those in the team, as well as the research funders (MRC and HTA Programme). Throughout the project, the team worked together to develop and refine the questions and the emerging conclusions. Bringing together this collection of people has been a research process in its own right, acting as a springboard for shaping the research. This methodological pluralism (multilensing) has resulted in a more informed and more expert position.

### Barriers to this research

There were two main barriers to this research. One was simply the amount of time and money

available to conduct the project. Working within the constraints of a fixed one-year grant and a fixed upper limit for funding, the present authors no doubt did what they were finding the STEPS trialists doing: making a good case for the work they would carry out, but possibly being unconsciously overambitious, in part to secure the initial competitive funding. The team was also working in the expectation, as stated in the commissioning brief, that “continuation into a second year may be possible, subject to review at 8 months based on emerging results”. In the event this additional funding was not forthcoming.

The second major constraint related to the work in Part B. As described in Chapter 3, this involved telephone interviews with trial coordinating staff and clinical investigators spread over the UK. Considerable unanticipated delays occurred owing to the need, first, to obtain MREC approval for the study, and second, to obtain permission from several trust R&D departments. (Again, this is likely to have parallels with difficulties experienced in trials that were reviewed, where unpredicted and unpredictable problems may have been caused by changes in the external environment, which were often outside their control.)

The need for MREC approval was unexpected and time consuming, but at least only required one central application. Permission from R&D departments was also unexpected and even more time consuming. It required a separate application for each trust in which a potential interviewee was based. The paperwork was extensive and non-standard, and included applications for honorary contracts and the need to provide references. The checks verged on the ludicrous, including completion of occupational health forms and even a suggestion of police checks. The process was labour intensive for the main Part B researcher, and added at least 4 months' delay to work on this part. Clearly, this is disproportionate to this type of research, which involves neither patients nor face-to-face contact. The implications, however, are that either this extra amount of time (and therefore funding) needs to be built into grant applications (and funders need to be aware of the need to raise the funding level to take these considerations into account), or these sorts of studies involving a geographical spread of interviewees will no longer be possible within time-limited and budget-capped research projects. This concern about disproportionate barriers to research is not specific to STEPS (see recent editorial<sup>100</sup> and corresponding papers).

## Implications for practice for trialists and funders

While not having sufficiently definitive results to make strong recommendations, the authors believe that the work in STEPS allows them to make some tentative suggestions, that people undertaking future trials ought at least to think about the different phases in the life of trials, and the need to put greater emphasis on the process of actually doing trials. This implies learning lessons from successful trial managers, with better training facilities in this important area. Applicants could be encouraged to predict more accurately the feasibility of meeting their planned target sizes and recruitment periods, and their needs for funding.

Funders need reciprocally to encourage more realistic applications, with the implication that, if the same total amount of money were to be available, fewer trials would be able to be funded, but the ones that were should be less likely to need further funding midway through the process. The authors would urge that funders' assessments should take into account not only the science but also the importance of the question and the likelihood of its being answered, bearing in mind the likely conduct of the trial. Part B suggested that successful trials were those able to weather storms that blew up, both because they had built up a firm and stable structure that was unlikely to be knocked off course, but also because they were able to be flexible enough to adapt to unexpected issues. Perhaps funders could assess this potential for agility in much the same way as interviewees for jobs are asked how they have dealt with or would tackle a difficult situation. Arguably, the trialists should also expect agility from funders. The complexity of large trials means that unanticipated difficulties are highly likely at some time in every trial. Funders should recognise this and be prepared to help, financially if necessary, if the causes are beyond the trialists' control. Both the MRC and the HTA Programme have developed increasingly proactive approaches to trial monitoring, and this could be extending to

monitoring expenditure and remodelling funding profiles in the light of developments and progress. Funders may also need a formal process of assessing the 'payback' of research<sup>101</sup> or 'the value of the information'<sup>102</sup> to be gained from funding the trial, against other calls on scarce resources. Ideally, this assessment would need to be kept under observation by funders efficiently monitoring ongoing trials.

## Implications for further research

The original application for Part B had aimed to look at a larger number of trials with different recruitment patterns. In consultation with the funders, the research team decided to concentrate first on multiple voices from four exemplar trials. To assess whether the conduct of the successful trials might be able to provide lessons for how other trials could be successful, further in-depth investigation into trials with different recruitment patterns (including 'failures') is necessary to understand whether the patterns seen in the successful trials differ or are similar. Furthermore, although the perceptions of people intimately involved with the trials are invaluable, the addition of the voices of independent members of DMCs and TSCs, who may be knowledgeable but have sufficient distance to be more objective, could add further insights.

Another area for further research involves extending the reference model developed in the CRASH trial (in which patients were mainly unconscious) to other settings, to see whether it needs refinement and adaptation for other trials. This may lead to the development of a checklist that could be used as an audit tool for addressing management factors. Research is also needed to assess whether its application can help as a diagnostic of any problem and hence to choose strategies that are the most likely to increase recruitment rates or other markers of the success of a trial. Finally, these and other strategies need to be formally evaluated for their effectiveness in a range of trials.





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### Contribution of authors

The application was written by the principal investigator, Marion Campbell (MC), with Adrian Grant (AG) and Vikki Entwistle (VE) in Aberdeen, Diana Elbourne (DE), Jo Garcia (JG), Claire Snowden (CS) and Ian Roberts (IR) in London, and David Francis (DF) in Brighton. The separate components of the research were each carried out predominantly by a subgroup of the collaboration. Part A was mainly carried out by MC, AG, Alison

McDonald (AM) and Rosemary Knight (RK), Part B by CS, JG and DE, and Part C by DF, IR. AM and RK extracted the data from the MRC and HTA Programme files for Part A, CS conducted and analysed the interviews for Part B, and DF conducted and analysed the interviews for Part C. MC, AG and DE mainly wrote Chapter 1, MC and AG mainly wrote Chapter 2, CS, JG and DE mainly wrote Chapter 3, DF, IR, DE, MC and AG mainly wrote Chapter 4, and DE and AG wrote Chapter 5.

The whole team met on several occasions and all contributed to the whole project.

### Papers published in other peer-review journals relating to this research project

McDonald A, Knight RC, Campbell MK, Entwistle VA, Grant AM, Cook JA, *et al.* What influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies. *Trials* 2006;7:9.

Snowden C, Elbourne DR, Garcia J, Campbell MK, Entwistle VA, Francis D, *et al.* Financial considerations in the conduct of multi-centre randomised controlled trials: evidence from a qualitative study. *Trials* 2006;7:34.







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# Appendix I

## Structure of current MRC and HTA Programme progress reports

### Clinical trials funded by the MRC

#### Draft template for steering committee agendas and reports

The Medical Research Council requires that independent steering committees are set up for every major trial that it funds, and that these committees should meet at least once a year and submit a report to the relevant research board. Presented below are guidelines on the information that should be provided by triallists for discussion at steering committee meetings and included in the steering committee's annual report. It is suggested that the headings listed below should provide a basis for the agenda of the meetings and form the template for the report. These headings may not be appropriate at every stage of an individual trial or for all trials.

|  | <b>Target</b><br>(date target set) | <b>Achieved</b><br>(date achieved) |
|--|------------------------------------|------------------------------------|
| 1. Name of trial   |                                    |                                    |
| 2. Grant no.   |                                    |                                    |
| 3. Sample size sought  |                                    |                                    |
| 4. Date recruitment started  |                                    |                                    |
| 5. Proposed date for recruitment end   |                                    |                                    |
| 6. Actual recruitment rate versus target rate<br>(by month/quarter)  |                                    |                                    |
| 7. Acceptance rate, as a proportion of<br>(i) those invited to participate and<br>(ii) if known, all eligible participants |                                    |                                    |
| 8. Quarterly/monthly forecasts of recruitment for the<br>planned remainder of the trial                                    |                                    |                                    |
| 9. Losses to follow-up,<br>(i) as a proportion of those entered and<br>(ii) per month/quarter                              |                                    |                                    |
| 10. No. for whom follow-up has been completed successfully<br>(or still being successfully followed up)                    |                                    |                                    |
| 11. Completeness of data collected   |                                    |                                    |
| 12. Any available results (pooled)   |                                    |                                    |
| 13. Any organisational problems  |                                    |                                    |
| 14. Issues specific to individual trials (to be specified by the<br>steering committee)                                    |                                    |                                    |



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**PROGRESS REPORT FOR A PRIMARY RESEARCH PROJECT**

*(All Sections Must Be Completed)*

| GENERAL                            |                                  |
|------------------------------------|----------------------------------|
| Project Number                     | Lead Applicant                   |
|                                    |                                  |
| Project Title                      |                                  |
|                                    |                                  |
| Name & Address of Host Institution |                                  |
|                                    |                                  |
| Project Information                |                                  |
| Start Date:                        | End Date:                        |
|                                    |                                  |
| Details of any extensions granted: |                                  |
|                                    |                                  |
| Draft Final Report Due Date:       |                                  |
|                                    |                                  |
| Progress Report Number:            | Progress Report Submission Date: |
|                                    |                                  |

**PROGRESS**

Summary of Project Progress to Date (specifically since the last report)

**RECRUITMENT**

Summary of Recruitment to Date (with respect to the project targets)

**This report must be accompanied by a graphical presentation of recruitment showing actual recruitment against target recruitment with fully labelled axes and data tables**

| <b>RETENTION</b>   |
|--|
| Summary of Follow-up to Date (with respect to the project targets)   |
|  |
| <b>This report must be accompanied by a graphical presentation of retention showing actual retention against target retention with fully labelled axes and data tables</b> |

| <b>ISSUES</b>  |
|--|
| Problems Encountered by the Project to Date (specifically since the last report)       |
|  |
| Adverse Events Encountered by the Project to Date (specifically since the last report) |
|  |



| <b>ORGANISATION</b>   |  |
|---|--|
| Changes to Protocol to Date (specifically since last report)          |  |
|   |  |
| Changes to Project Staff to Date (specifically since the last report) |  |
|   |  |
| Trials Steering Committee and Data Monitoring & Ethics Committee      |  |
| Does the Project have a Trials Steering Committee?                    | Yes <input type="checkbox"/> No <input type="checkbox"/> |
| Does the Project have a Data Monitoring & Ethics Committee?           | Yes <input type="checkbox"/> No <input type="checkbox"/> |
| If 'No' briefly explain why the committee has not been formed:        |  |
|   |  |

| <b>PUBLICATIONS</b>  |  |
|--|--|
| Project Outputs Submitted for Publication (specifically since last report) |  |
|  |  |

Conference Presentations and Media Interviews (specifically since the last report)

Acknowledgements

|  |     |                          |    |                          |
|--|-----|--------------------------|----|--------------------------|
| Have all outputs included the NHS Disclaimer?            | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |
| Have all outputs acknowledged HTA sponsorship?           | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |
| Have copies of all outputs been forwarded to the NCCHTA? | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |

If 'No' briefly explain why:

**REPORTING**

Actions Recommended by the TSC/DMEC to Date (specifically since the last report)

Matters Relating to Consumer Involvement to Date (specifically since the last report)





# Appendix 2

## Part A: data extraction form

(see Appendix 3 for definitions)

### A. TRIAL IDENTIFYING DETAILS

Title

\_\_\_\_\_

\_\_\_\_\_

Acronym

\_\_\_\_\_

Grant no.

ISRCTN no.

(if available)

\_\_\_\_\_

\_\_\_\_\_

PI details

Name:

\_\_\_\_\_

Address:

\_\_\_\_\_

\_\_\_\_\_

E-mail:

\_\_\_\_\_

Tel:

\_\_\_\_\_

Fax:

\_\_\_\_\_

### B. ADMINISTRATIVE DETAILS

**Day**      **Month**      **Year**

Date of grant application submission:

/   /

Funding started:

/   /

Recruitment started:

/   /

Predicted recruitment closed:

/   /

Actual recruitment closed:

/   /

Date of first MREC approval (if appropriate):

/   /

Date of first LREC approval (if available):

/   /

Date of last LREC approval (if available):

/   /

**C. TRIAL FEATURES**

**C1 Was there a pilot or feasibility phase?** Yes  No  Not clear

*If yes, was this funded?* Yes  No  Not clear

**C2 Was the recruitment strategy changed on the basis of the pilot?** Yes  No  Not clear

*If yes, please give details*

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**C3 Which disciplines did the applicants represent?**

Medical  Nursing  Economics  Statistics  HSR  Consumers  Other   
 /Dental  /PAMS

*If other, please give details*

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**C4 Where was the trial coordinated from?**

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**Is this a Trials Unit?** Yes  No

**C5 Was there a dedicated trial manager?** Yes  No  Not clear

**C6 Were there paid local trial staff?** Yes  No  Not clear

Please give details about staffing (*include disciplines, no. of sessions worked, etc.*)

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C7 Were consumers involved? Yes  No  Not clear

If yes, please describe \_\_\_\_\_

If yes, at what stages (e.g. grant application, protocol design, during retention period, throughout)?

C8 Were there any recruiting centres outside the UK? Yes  No

(If subtrials within the one study split here)

C9 Design (preference, cross-over, parallel, factorial, Latin square, cluster) \_\_\_\_\_

C10 Number of arms \_\_\_\_\_

C11 Clinical area (categories) \_\_\_\_\_

C12 Which of these settings were crucial to recruitment?

Community  General practice  Hospital  Mixed

C13 What was the geographical spread of the recruiting sites?

Regional  Multiple

C14 Interventions (surgical, medical, etc.) \_\_\_\_\_

C15 Were all the interventions available outside the trial? Yes  No  Not clear

C16 Inclusion criteria (age, etc.) \_\_\_\_\_

**D. RECRUITMENT**

D1 What was the original recruitment target?

D2 Was the target revised during the trial? Yes  No

If yes, what was the revised target?

D3 What was the final recruitment figure?

D4 Was the final recruitment figure?  Over original target  
 To original target  
 Above revised target  
 To revised target  
 Under revised target  
 Under original target

D5 Was there a request made for an extension to the trial grant to complete the original trial?  Yes  No

*If yes*, was there a time extension or supplementary grant to the trial awarded?  Yes  No

*If yes*, was the extension  time only?  No  
 supplementary grant only?  No  
 time and supplementary grant?  No

How many extensions were there?

Please give further details (length of extension, etc.)  
 \_\_\_\_\_  
 \_\_\_\_\_

**E. FINANCE**

What was the original award? £ \_\_\_\_\_  
 What was the supplementary award(s), if any £ \_\_\_\_\_  
 £ \_\_\_\_\_  
 £ \_\_\_\_\_  
 £ \_\_\_\_\_  
 £ \_\_\_\_\_

**F. DESCRIPTION OF COMPONENTS OF DELAY OR FAILURE TO REACH RECRUITMENT TARGET**

**CENTRE RECRUITMENT**

F1 Was the overall start to recruitment delayed? Yes  No

If yes, by how long? \_\_\_\_\_  
 \_\_\_\_\_



If yes, to what were any reasons related?

|                     |                          |                             |                          |
|---------------------|--------------------------|-----------------------------|--------------------------|
| Funding issues      | <input type="checkbox"/> | R&D                         | <input type="checkbox"/> |
| Central staff       | <input type="checkbox"/> | Local research staff        | <input type="checkbox"/> |
| MREC                | <input type="checkbox"/> | Local clinical arrangements | <input type="checkbox"/> |
| LRECs               | <input type="checkbox"/> | Other                       | <input type="checkbox"/> |
| No reason available | <input type="checkbox"/> |                             |                          |

**Please give details of reasons for delay and actions specified**

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**F2 Were any centres pre-identified in the application?**

Yes  No  Not clear   
*(if no go to question F5)*

**IF YES,**

**F3 Was there a failure to bring in any pre-planned centres (after first had started)?**

Yes  No  Not appropriate

If yes, to what were any reasons related?

|                             |                          |                     |                          |
|-----------------------------|--------------------------|---------------------|--------------------------|
| LREC                        | <input type="checkbox"/> | Centre changed mind | <input type="checkbox"/> |
| R&D                         | <input type="checkbox"/> | Other               | <input type="checkbox"/> |
| Local research staff        | <input type="checkbox"/> | No reason available | <input type="checkbox"/> |
| Local clinical arrangements | <input type="checkbox"/> |                     |                          |

**Please give details of reasons for failure and actions specified**

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**F4** Were there delays in bringing in any pre-planned centre (after first had started)? Yes  No

*If yes, to what were any reasons related?*

|   |  |
|---|--|
| LREC <input type="checkbox"/>                 | Local clinical arrangements <input type="checkbox"/> |
| R&D <input type="checkbox"/>                  | Other <input type="checkbox"/>                       |
| Local research staff <input type="checkbox"/> | No reason available <input type="checkbox"/>         |

Please give details of reasons for delay and actions specified \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

**F5** Did new centres have to be recruited? Yes  No

*If yes, please give details (number of new centres, length of recruiting period, etc.).*

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

**What had to be done to bring in more?** \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

**F6** In total, how many centres finally 'signed up' to the trial?

**F7** How many centres signed up but did not recruit any participants?

**F8** How many centres had a delayed start?

Please describe these delays in starting \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_



Please give details of reasons and actions specified

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b) If there was a difference between recruitment at different sites please give details

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F13 Was overall recruitment lower than expected? Yes  No

*If yes, did this reflect early/late recruitment problems?*

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F14 Were there any marked changes in the recruitment rate over time? Yes  No

*If yes, please give details and indicate any reported reasons for this*

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---

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F15 Was recruitment stopped early? No  In several sites   
In one site  In all sites

*Please give details and indicate any reported reasons for this (e.g. DMC decision)*

---

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**F16** Are there any records of attempts to improve recruitment?      Yes      No      Not clear  
           

**Please give details** \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**Any other comments/interesting features** \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_



## Appendix 3

### Part A: data extraction form definitions

#### Section A: Trial identifying details

Descriptive details only

PI: the most recent contact details are recorded, not necessarily those on the grant application.

#### Section B: Administrative details

Date of grant application submission – date that PI signed the application.

MREC approval: date that the MREC first approved the trial, not subsequent protocol amendment approvals.

LREC approvals: date of first and last LREC approvals. There could be quite a time lapse between these dates if new centres were recruited.

#### Section C: Trial features

- C1** Pilot phase: include either pilot or feasibility phase that addressed anything to do with recruitment (including changes to trial documentation).
- C3** Disciplines
  - medical, including dental
  - PAMS: professions allied to medicine (nurses, physiotherapists, occupational therapists, etc.)
  - HSR: including sociologists, psychologists and generic methodologists
  - consumers: including any representation by consumers/consumer bodies
  - multidisciplinary: medical/dental/nursing plus at least one other discipline.
- C4** Trials unit: defined as a unit coordinating more than one trial.
- C5** Trial manager: defined as a person responsible for the day-to-day coordination.
- C6** Local trial staff are paid, dedicated and involved in recruitment.
- C7** Consumer involvement is defined as what the trial thought represented consumer involvement.
- C8** To be eligible for inclusion in the study, at least one recruiting centre must be in the UK.
- C9** Design: cluster trials excluded.
- C11** Clinical area: categories will be developed, but likely to include cancer, child health,

primary health, complementary health, mental health, cardiovascular and cerebrovascular (see MRC disease areas at end of document).

**C13** Regional is one county/region only.

**C16** Main inclusion criteria included.

#### Section D: Recruitment

- D5** Include extensions to complete original trial only. Extensions to carry out any supplementary methodological work not included. Include extensions to submit final report if delay has been due to recruitment phase being extended.

#### Section E: Finance

#### Section F: Components of delay/failure to reach recruitment target

- F1** Once funding had started.
- F2** Preplanned centres are defined as sites that were identified at the time the grant was awarded.
- F5** New centres are those not identified at the start of the trial.
- F6** Based on what the trial treated as individual sites.
- F8** Centres with a delayed start: this is defined as being relevant to their planned start, not relative to the start of the trial.
- F9** First 25% of recruiting time is approximate only. It is specific to the early recruitment period.

#### MRC disease areas

1. Cancer
2. Cardiovascular
3. Dental
4. Diabetes
5. Gastroenterology
6. Gerontology
7. Hearing research
8. HIV/AIDS

- 9. Incontinence
- 10. Leukaemia
- 11. Multiple
- 12. Neurosciences/psychiatry
- 13. Obstetrics and gynaecology
- 14. Ophthalmology
- 15. Orthopaedics/rheumatology
- 16. Plastic surgery

- 17. Primary care
- 18. Public health/social medicine
- 19. Renal
- 20. Respiratory disease
- 21. Surgical
- 22. Training fellowship
- 23. Tropical medicine research



## Appendix 4

### Part B: letter for potential interviewees for MREC application (*adapted for each trial*)

MREC/03/4/102, version 2, 4th November 2003)

Address

Date

Dear Dr .....

**Re: Study recruitment to clinical trials**

I am writing with regard to some research which involves staff previously or currently connected to the XXX Unit at the YYY Hospital and involved in the ZZZ trial. The research assesses factors associated with recruitment to randomized controlled trials and is funded by the Department of Health's Health Technology Assessment Programme and the Medical Research Council. It is being carried out by researchers at the Universities of Aberdeen, London, Brighton and Cambridge. As part of this project we are carrying out a qualitative sub-study to examine the views of those involved in a number of trials, one of which is the ZZZ Trial. It involves interviews with medical staff who have had some experience of recruiting to this trial. As you were involved in the recruitment of some patients to the ZZZ Trial we would like to ask you to take part in the research.

The interviews will explore clinicians' opinions about the trials, highlighting any specific features which may have helped or hindered the recruitment process. The interview will not include discussion of individual patients and we must ensure that there is no disclosure of information about individual patients in the course of the interview. With your permission the interview would be tape-recorded. The tape will be transcribed by a transcribing company which has been used and trusted by the researchers for over 5 years. It would be marked confidential and a study number rather than your name would be used to identify the tape. The opinions expressed in interview will be treated as confidential although of course we would aim to use non-attributed comments in any publications that are written. You would be asked after the interview to complete a one page demographic questionnaire.

There is a reply slip and prepaid envelope with this letter if you want to let me know whether or not you are interested in taking part in the study. Alternatively you could email me if that is convenient, at cms1000@cam.ac.uk. As we are working to a tight schedule, I will call you some time in the next week or so unless I hear that you would prefer not to take part. In the meantime if you wish to know more about the research you could call on the above number or email me and I would be happy to answer any queries you have.

Yours sincerely

Claire Snowdon  
Research Fellow .....



## Appendix 5

### Part B: information sheet for potential interviewees for MREC application (adapted for each trial)

**Information Sheet (MREC/03/4/102, version 2, 4th November 2003)**

**A qualitative study of the professionals' views of recruitment patterns associated with four MRC/HTA trials: in-depth analysis of purposively selected case studies**

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

**What is the purpose of the study?**

As part of a larger project which is assessing factors associated with recruitment to trials, we are carrying out a qualitative sub-study to examine the views of those involved in a number of randomised controlled trials, one of which is the [name] Trial. The study is due for completion at the end of March 2003.

**Why have I been chosen and do I have to take part?**

The qualitative study involves interviews with medical staff who have had some experience of recruiting to this trial. As you were involved in the recruitment of some patients to the [name] Trial we would like to ask you to take part in the research. Within the current funding we will be carrying out approximately 30 interviews. It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason.

**What will happen to me if I take part?**

The clinicians that decide to take part in the study will be interviewed either by telephone or in person. The interviews will explore clinicians' opinions about the trials, highlighting any specific features which may have helped or hindered the recruitment process. The interview will not include discussion of individual patients and we must ensure that there is no disclosure of information about individual patients in the course of the interview. Interviewees would be asked to complete a one page demographic questionnaire. Once the interview and questionnaire are completed, no further assistance with the study would be required.

With your permission the interview will be tape-recorded. The tape will be transcribed by a transcribing company which has been used and trusted by the researchers for over 5 years. All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the Centre for Family Research will have your name and address removed so that you cannot be recognised from it. The opinions that you express in interview will be treated as confidential although of course we would aim to use non-attributed comments in any publications that are written. For individuals with specific roles within trials, e.g. Principal Investigator or trial manager, it is possible that you may be identified because your name is connected with a specific trial in the public domain. We will take every step we can to use data sensitively for this study.

**What will happen to the results of the research study?**

The results of this research are likely to be published in 2004/5 although a report will be available at an earlier date. Our usual policy is to send a copy of the results to interviewees. If your contact details are likely to change you may wish to give us an alternative address if you do wish to have a copy of the findings.

**Who is organising and funding the research?**

The research is funded by the Health Technology Assessment Programme and Medical Research Council.

**Who has reviewed the study?**

The study has been reviewed by the Health Technology Assessment Programme and the Medical Research Council and their external reviewers, and by Trent Multicentre Research Ethics Committee, reference 03/4/102, date of review 2/10/03.

**Contact for Further Information**

If you require any further information about the study you can contact either of the following:

Claire Snowdon  
Research Fellow  
Centre for Family Research  
Free School Lane  
Cambridge CB1 8NL  
Tel 01223 334508  
cms1000@cam.ac.uk

Diana Elbourne  
London School of Hygiene & Tropical Medicine  
Keppel Street  
London WC1E 7HT  
Tel. 0207 927 2230  
diana.elbourne@lshtm.ac.uk

**What do I do now?**

There are two copies of a consent form and prepaid envelope with this letter. In accordance with MREC approval, if you wish to take part in the study you should sign and keep one copy of the form, and sign and return the second copy to

me. If you do not wish to take part in the study you could indicate this on the form, or email the Research Fellow, Claire Snowdon, at cms1000@cam.ac.uk, or call her on 01223 334508. As the study is working to a tight schedule, she will aim to call you to discuss possible participation in the study some time in the next week or so, unless she hears from you that you would prefer not to take part.

**What if I have any concerns?**

If you have any concerns or other questions about this study or the way it has been carried out, you should contact Professor Marion Campbell, Principal Investigator for the study, or you may contact Wendy Surridge at the London School of Hygiene and Tropical Medicine. The contact details are:

Marion Campbell  
Health Services Research Unit (HSRU)  
Polwarth Building  
Foresterhill  
University of Aberdeen  
Aberdeen AB25 2ZD  
Tel. 01224 554480  
m.k.campbell@abdn.ac.uk

Wendy Surridge  
Registrar  
London School of Hygiene & Tropical Medicine  
Keppel Street  
London WC1E 7HT  
Switchboard: +44 (0)20 7636 8636  
Fax: +44 (0)20 7436 5389

*This information sheet is for you to keep*

# Appendix 6

## Part B: consent form for potential interviewees for MREC application (adapted for each trial)

**CONSENT FORM**

Centre Number: :  
 Study Number: MREC/03/4/102, version 2, 4th November 2003  
 Interviewee Identification Number:

**Title of Project: A qualitative study of the professionals' views of recruitment patterns associated with four MRC/HTA trials: in-depth analysis of purposively selected case studies (MREC/03/4/102, version 2, 4th November 2003)**

Name of Researcher: Claire Snowdon

Please initial box

- 1. I confirm that I have read and understand the information sheet dated .....  
 (version .....) for the above study and have had the opportunity to ask questions. [ ]
- 2. I understand that my participation is voluntary and that I am free to withdraw at any time,  
 without giving any reason, without my legal rights being affected. [ ]
- 3. I agree/do not agree to take part in the above study (delete as appropriate).

|                     |           |      |
|---------------------|-----------|------|
| Name of interviewee | Signature | Date |
|---------------------|-----------|------|

|            |           |      |
|------------|-----------|------|
| Researcher | Signature | Date |
|------------|-----------|------|

Please retain a copy for yourself and send a second copy to Claire Snowdon in the prepaid envelope provided

Other collaborators for Level 1 and Level 3 are:

**Level 1**  
 Vikki Entwistle  
*Reader/Programme Director (Participation in Health Care)*  
*Health Services Research Unit, University of Aberdeen*  
 email v.a.entwistle@abdn.ac.uk

Alison McDonald  
*Health Services Research Unit, University of Aberdeen*  
 Tel. 01224 554338  
 email a.mcdonald@abdn.ac.uk

Rosemary Knight  
 Research Co-ordinator  
 Medical Statistics Unit, London School of Hygiene and Tropical Medicine  
 Tel. 020 7927 2473  
 email rosemary.knight@lshtm.ac.uk

**Level 3**  
 David Francis  
 Brighton  
 email d.l.francis@brighton.ac.uk



## Appendix 7

### Part B: interview schedule for the FOCUS the central office staff (PIs and trial managers) for MREC application (*adapted for each trial*)

#### Draft interview schedule for the FOCUS trial central office staff (PIs and trial managers)

This study involves four trials and there will be specific areas of the interview that will be driven by the individual conditions of those trials. The study involves professionals with a variety of roles within the trials, at the central trial office level (principal investigators, trial managers) and a recruiting centre level (local lead investigators, local recruiters) and the questions will vary for each of these individuals. Rather than producing 16 variants on the schedule, and given the semi-structured nature of our approach, we will limit the schedule to two approaches (trial office and recruiting centre) and anticipate a degree of flexibility within these. Although specific questions are given in the schedule, it is likely that the interview will develop over time. There is a school of thought within qualitative methods which permits adaptation of each interview in response to the insights gained in the previous interview, and so new lines of enquiry emerge as the interviewer grows in their understanding of the phenomenon.

We plan to interview professionals associated with the FOCUS trial first, using a themed approach, guided by the research recommendations in Ross *et al.* 1999 (Barriers review), of which one of our team (Adrian Grant) is an author.

Ross *et al.* recommend that research is needed in our areas and these are reflected in the schedule:

- Area 1 – to identify robust scientific trial designs which are compatible with routine medical care and which are attractive to clinicians and patients
- Area 2 – to ascertain the optimum structure, staffing and organisation for the conduct of RCTs

Area 3 – to understand the problems experienced and solutions experienced in current RCTs

Area 4 – to understand more clearly the reasons why clinicians and patients do or do not take part in RCTs

The asterisks denote questions that are driven by our findings from Level 1 (\*) and from Level 3 (\*\*\*) to allow some cross-reference and comparison of data from the various parts of the study.

#### Interview schedule

##### Developmental stages of the trial

Would you briefly describe the early history of the FOCUS trial, explaining why it was necessary and what it was intended to achieve? \*

How easy or difficult was it to gain support for the trial in the developmental stages (i.e. academic, clinical, financial support)? Were there any particular methods you used? \*\*\*

At that stage, did you feel that there were any factors which would aid the progress of this trial?

At that stage, what did you feel were the possible obstacles for this trial which would have to be overcome? \*\*\*

Were there any procedures put in place to deal with these factors/obstacles? \*\*\*

Did you carry out a pilot study? If yes, was this funded? If yes, did it result in any changes to your recruitment strategies? \*

Did you involve consumers in the developmental, or any other stage, of the trial? \*

Who is responsible for recruitment, and are they paid to do so? (per recruitment/flat fee)\*

**Area 1: identify robust scientific trial designs which are compatible with routine medical care and which are attractive to clinicians and patients**

What is the scientific design of the FOCUS trial? (preference, parallel, multifactorial, other). How many arms are there?

Do you feel that this trial has a particularly robust scientific design?

How does the design of the trial fit with routine clinical care?

What is your impression of how clinicians view

- the scientific design of the trial
- the importance of the trial
- the impact of the trial on their patients?

What is your impression of how patients view

- the scientific design of the trial
- the importance of the trial
- the impact of the trial on themselves?

*For each trial at this point it would be appropriate to insert questions which are relevant to what we will come to know about each of the four trial designs, e.g. impact of use of placebo/comparison with standard care, cross-over designs, on recruitment.*

**Area 2: structure, staffing and organisation for the conduct of the FOCUS trial**

Could you describe how the trial works at a central, trial office level, and at the level of the local coordinators/recruiters?

Has this structure/organisation been successful?

How do you see the role of the

- PI
- trial manager
- local lead investigator
- local recruiter?

Who do you see as being responsible for promotion of recruitment in the FOCUS trial?

How do you see the role of the

- PI
- trial manager
- local lead investigator
- local recruiter?

Do you think there is a general ‘trial ethos’ in your centre? If yes, how does this manifest itself?

To what extent has communication between the central trial office and the centres been successful?

**Area 3: to understand the problems experienced and solutions experienced in current RCTs**

What have been the biggest challenges for the FOCUS trial?

How have these challenges been addressed? With what degree of success?

We would like you to outline the progress of recruitment to the trial, but first we need to place the FOCUS trial in the same categories of recruitment in trials as used in our epidemiological review. Before describing the progress of recruitment it would help if you could simply state which category represents the FOCUS trial.

- Recruitment lower/not lower than expected
- Marked change/no marked change in recruitment
- Recruitment stopped early/finished on time/required an extension
- Recruitment target revised/not revised during the trial.\*

Do you know what percentage of your original target has been recruited?\*

Now please expand on the progress of recruitment.

If you required an extension, please give details.

(If not covered by previous questions) Were there any particular methods that you used to promote recruitment? If yes, what was the basis of these (research literature, previous experience, novel approach)? How successful were they?\*

How do you think this trial fitted with clinical practice?

How do you think patients have responded to the trial?

How do you see the process of recruitment itself for the FOCUS trial? Do you think there have been any factors which have helped or hindered?

(If not already covered) What do you feel have been the **key** factors which have contributed to the trial’s difficulties with or success in recruitment?



**Area 4: to understand more clearly the reasons why clinicians and patients do or do not take part in RCTs**

Why do you think clinical colleagues have elected to participate in the FOCUS trial?

Why do you think patients have entered the trial?

We are interested to compare the views of our interviewees on the relative importance of factors which might be a barrier to recruitment in your trial, as identified in a major review of the literature. To allow a comparison could you give a number, from 0 (not important) to 5 (very important), as you would in a questionnaire, for each of the factors listed. We would then like you to expand on the reasons for your choice, which we can discuss after you have identified a number.

In terms of the clinicians involved in the FOCUS trial, how important a barrier to recruitment do you think the following factors were/are:

- Time constraints
- Lack of staff and training
- Worry about the impact on the doctor/patient relationship
- Concern for patients
- Loss of professional autonomy
- Difficulty with the consent procedure
- Lack of rewards and recognition
- Insufficiently interesting question?

In terms of the patients offered recruitment to the FOCUS trial, how important a barrier to recruitment were/are:

- Additional procedures and appointments for the trial
- Travel problems and costs
- Patient preferences for a particular treatment (or no treatment)
- Worry about uncertainty of treatment or trial
- Concern about information and consent
- Difficulties with the protocol
- The influence of their clinician?

**Level 3 questions**

*For the STEPS Projects we have been investigating how trials management may or may not benefit from theories developed in a marketing context, i.e. how techniques developed to improve marketing of organisations might be used to improve accrual to trials. We would be interested to know whether or not any of the ideas from marketing are already being used, but possibly with a different slant or label. We may already have covered some of this material earlier in the interview in which*

*case you can just refer me back to our previous discussion:*

Could you tell us if you have used any of the following approaches:

Did you ever define the distinctive contribution that your trial would make?

If yes:

- Was this written down?
- How and to whom was it communicated?
- Did it have any effect on your planning of the trial?

Did you have any methods of making sure that your trial was seen as worthwhile?

Did you have any methods of maintaining its profile among relevant groups?

How did you identify possible hindrances to the trial, or areas where people may be resistant? How did you deal with these problems and what was the effect of your intervention?

Did you have particular individuals who represented and defended the trial – in the world of marketing they would be called sponsors or champions?

If yes:

- How did you enrol and motivate them?
- Was it successful?

Did you have any strategies for making the trial as undemanding as possible for colleagues and patient participants?

If yes:

- Did you experiment or modify any of the procedures in the light of feedback?
- By the end of the trial were you still using the same procedures?

*Optional prompt* – Did you have any ways of making it easy for clinicians and patients to incorporate the requirements of the trial into their other routines?

Did you involve any advertising or marketing people for your trial?

Did you identify the points at which people could opt in or opt out (decision points) of involvement

with the trial? Did you employ any means of increasing the likelihood that they would choose to opt in to the trial?

Did you have any means of recognising or rewarding professional and patient participation?

### **Retrospective and overview**

What would you take from the FOCUS trial and use in another setting? And why?

What would you not take from this trial and use in another setting? And why?

What do you consider to be the key factors in the success of this trial? And why?

This discussion has obviously focused on the FOCUS trial, but I would be interested to hear whether you think the FOCUS trial is very typical of the trials you coordinate or whether you have more general comments based on your experience in other trials.

### **Reference**

Ross S, Grant A, Counsell C, Gillespie W, Russell IT, Prescott R. Barriers to participation in randomised controlled trials: a systematic review. *J Clin Epidemiol* 1999;**52**:1143–56.

## Appendix 8

### Part B: interview schedule for the FOCUS trial recruiting centre staff for MREC application (adapted for each trial)

#### Draft interview schedule for the FOCUS trial for recruiting centre staff

This study involves four trials and there will be specific areas of the interview that will be driven by the individual conditions of those trials. The study involves professionals with a variety of roles within the trials, at the central trial office level (principal investigators, trial managers) and at recruiting centre level (local lead investigators, local recruiters) and the questions will vary for each of these individuals. Rather than producing 16 variants on the schedule, and given the semi-structured nature of our approach, we will limit the schedule to two approaches (trial office and recruiting centre) and anticipate a degree of flexibility within these. Although specific questions are given in the schedule, it is likely that the interview will develop over time. There is a school of thought within qualitative methods which permits adaptation of each interview in response to the insights gained in the previous interview, and so new lines of enquiry emerge as the interviewer grows in their understanding of the phenomenon.

We plan to interview professionals associated with the FOCUS trial first, using a themed approach, guided by the research recommendations in Ross *et al.* 1999 (Barriers review), of which one of our team (Adrian Grant) is an author.

Ross *et al.* recommend that research is needed in 4 areas and these are reflected in the schedule:

- Area 1 – to identify robust scientific trial designs which are compatible with routine medical care and which are attractive to clinicians and patients
- Area 2 – to ascertain the optimum structure, staffing and organisation for the conduct of RCTs

Area 3 – to understand the problems experienced and solutions experienced in current RCTs

Area 4 – to understand more clearly the reasons why clinicians and patients do or do not take part in RCTs.

The asterisks denote questions that are driven by our findings from Level 1 (\*) and from Level 3 (\*\*\*) to allow some cross-reference and comparison of data from the various parts of the study.

#### Interview schedule

##### Early stages of the trial

Would you briefly describe the FOCUS trial, explaining why it was necessary and what it was intended to achieve?

How easy or difficult was it to gain support for the trial in your centre?

At that stage, did you feel that there were any factors which would aid the progress of this trial?

At that stage, what did you feel were the possible obstacles for this trial which would have to be overcome?

Were there any procedures put in place to deal with these factors/obstacles?

##### **Area 1: identify robust scientific trial designs which are compatible with routine medical care and which are attractive to clinicians and patients**

What is the scientific design of the FOCUS trial? (preference, parallel, multifactorial, other). How many arms are there?

Do you feel that this is a particularly robust scientific design?

How does the design of the trial fit with routine clinical care?

What is your impression of how clinicians view  
– the scientific design of the trial  
– the impact of the trial on their patients?

What is your impression of how patients view  
– the scientific design of the trial  
– the impact of the trial on themselves?

*For each trial at this point it would be appropriate to insert questions which are relevant to what we will come to know about each of the four trial designs, e.g. impact of use of placebo/comparison with standard care, cross-over designs, on recruitment.*

### **Area 2: structure, staffing and organisation for the conduct of the FOCUS trial**

Could you describe how the trial works at a central, trial office level, and at the level of the local coordinators/recruiters?

Has this structure/organisation been successful?

How do you see the role of the

- PI
- trial manager
- local lead investigator
- local recruiter?

Who do you see as being responsible for promotion of recruitment in the FOCUS trial?

Do you think there a general 'trial ethos' in your centre? If yes, how does this manifest itself?

To what extent has communication between the central trial office and your centre been successful?

### **Area 3: to understand the problems experienced and solutions experienced in current RCTs**

What have been the biggest challenges in your centre for the FOCUS trial in your centre? Are these different to the ones you feel were faced by the trial more generally?

How have these challenges been addressed in your centre? With what degree of success?

Would you outline the progress of recruitment to the trial in your centre?

(If not covered by previous questions) Were there any particular methods that you used to promote recruitment? If yes, what was the basis of these

(research literature, previous experience, novel approach)? How successful were they? Were these independent of the trial office or in response to a recruitment directive?

How has this trial fitted with your usual clinical practice?

How have patients responded to the trial?

How have you found the process of recruitment itself? Have there been any factors which helped or hindered?

(If not already covered) What do you feel have been the **key** factors which have contributed to your own centre's difficulties with or success in recruitment?

### **Area: to understand more clearly the reasons why clinicians and patients do or do not take part in RCTs**

Why did you elect to participate in the FOCUS trial?

Why do you think patients have entered the trial?

We are interested to compare the views of our interviewees on the relative importance of factors which might be a barrier to recruitment in your trial, as identified in a major review of the literature. To allow a comparison could you give a number, from 0 (not important) to 5 (very important), as you would in a questionnaire, for each of the factors listed. If you wish to expand on the reasons for your choice, we can discuss that after you have identified a number

In terms of the clinicians involved in the FOCUS trial in your centre, how important a barrier to recruitment was/is:

- Time constraints
- Lack of staff and training
- Worry about the impact on the doctor/patient relationship
- Concern for patients
- Loss of professional autonomy
- Difficulty with the consent procedure
- Lack of rewards and recognition
- Insufficiently interesting question?

In terms of the patients offered recruitment to the FOCUS trial in your centre, how important a barrier to recruitment was/is:

- Additional procedures and appointments for the trial

- Travel problems and costs
- Patient preferences for a particular treatment (or no treatment)
- Worry about uncertainty of treatment or trial
- Concern about information and consent
- Difficulties with the protocol
- The influence of their clinician?

### **Retrospective and overview**

What would you like to see taken from the FOCUS trial and used in another setting? And why?

What would you not like to see taken from this trial and used in another setting? And why?

What do you consider to be the key factors in the success of this trial? And why?

This discussion has obviously focused on the FOCUS trial, but I would be interested to hear whether you think the FOCUS trial is very typical of the trials that you are involved in or whether you have more general comments based on your experience in a range of trials.

Is there anything else that you would like to add about the FOCUS trial?

### **Reference**

Ross S, Grant A, Counsell C, Gillespie W, Russell IT, Prescott R. Barriers to participation in randomised controlled trials: a systematic review. *J Clin Epidemiol* 1999;**52**:1143–56.





# Health Technology Assessment reports published to date

## Volume 1, 1997

### No. 1

Home parenteral nutrition: a systematic review.

By Richards DM, Deeks JJ, Sheldon TA, Shaffer JL.

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Professor Rudy Bilous, Professor of Clinical Medicine & Consultant Physician, The Academic Centre, South Tees Hospitals NHS Trust

Ms Dea Birkett, Service User Representative, London

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Professor Paul Glasziou, Director, Centre for Evidence-Based Practice, University of Oxford

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Dr Susanne M Ludgate, Clinical Director, Medicines & Healthcare Products Regulatory Agency, London

Mr Stephen Pilling, Director, Centre for Outcomes, Research & Effectiveness, Joint Director, National Collaborating Centre for Mental Health, University College London

Mrs Una Rennard, Service User Representative, Oxford

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Dr Margaret Somerville, Director of Public Health Learning, Peninsula Medical School, University of Plymouth

Dr Graham Taylor, Scientific Director & Senior Lecturer, Regional DNA Laboratory, The Leeds Teaching Hospitals

Professor Lindsay Wilson Turnbull, Scientific Director, Centre for MR Investigations & YCR Professor of Radiology, University of Hull

Professor Martin J Whittle, Clinical Co-director, National Co-ordinating Centre for Women's and Childhealth

Dr Dennis Wright, Consultant Biochemist & Clinical Director, The North West London Hospitals NHS Trust, Middlesex

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Ms Anne Baileiff, Consultant Nurse in First Contact Care, Southampton City Primary Care Trust, University of Southampton

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Mrs Sharon Hart, Consultant Pharmaceutical Adviser, Reading

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Dr Richard Tiner, Medical Director, Medical Department, Association of the British Pharmaceutical Industry, London



## Therapeutic Procedures Panel

### Members

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| <p>Dr Mahmood Adil, Deputy<br/>Regional Director of Public<br/>Health, Department of Health,<br/>Manchester</p> <p>Dr Aileen Clarke,<br/>Consultant in Public Health,<br/>Public Health Resource Unit,<br/>Oxford</p> |   |   |  |

## Disease Prevention Panel

### Members

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***We look forward to hearing from you.***