An Investigation of Practice and Practitioner Factors that Influence the Recruitment of Patients to Primary Care Based Randomised Controlled Trials: Case Study of the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) Study

by

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Abstract

Background:

Patient recruitment to trials is problematic; many fail to achieve targets, leaving them underpowered and unable to address their hypothesis. Few solutions have been identified in existing literature. This thesis aimed to: identify factors associated with recruitment; and understand clinicians' experiences of recruiting patients to a primary care based randomised controlled trial (RCT). This was explored using The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial as a case study.

Methods:

Mixed methods were used: a systematic review to identify factors influencing recruitment to primary care based RCTs; quantitative analysis of BAFTA data to identify factors associated with recruitment; and qualitative interviews with General Practitioners involved with BAFTA, to understand their experience of participation.

Results:

Existing literature demonstrated that influences on recruitment include: study workload; study question; concerns about patients. Recommendations to address these issues are not based on strong empirical evidence. BAFTA identified factors associated with patient recruitment (practice size; GP age; recruitment year); and patterns over time. Interviews identified differences in attitude between high and low recruiters, including risk perception and motivation.

Conclusions:

This thesis demonstrates how practitioners can influence patient recruitment. Revised recruitment methods need testing in prospective trials.

Acknowledgements

I am indebted to my family for the support they have given me over the years it has taken to complete this thesis, especially to my children for their patience when every weekend seemed to be taken over by work. Thanks Charlotte and Natalie, you are finally going to get your mum back. Thanks also to my husband, Julian Fletcher, for all the cooking he did while I was writing! Many thanks also to my mum, Paulette Robinson, not only for her encouragement and many hours of childcare, but also for proof reading this final version.

I would like to acknowledge the help of my supervisors, Jonathan Mant and Helen Lester, for their invaluable advice, support and encouragement, and the rapidity and depth of their feedback. Without them I doubt this would have ever been completed. I also thank my colleagues, Kathleen Waldron, for the many hours she spent transcribing the interviews, and Phil Dimmock, who kindly volunteered his time to proof read this final version.

Finally, I would like to thank all the GPs who gave up their time to be interviewed for this study. Without them, this thesis would not have been possible.

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Abbreviations

AF	Atrial Fibrillation
BAFTA	Birmingham Atrial Fibrillation Treatment of the Aged Study
CET	Cognitive Evaluation Theory
CRF	Case Report Form
ECG	Electrocardiogram
EMR	Electronic Medical Record
GCP	Good Clinical Practice
GMC	General Medical Council
GP	General Practitioner
ICHGCP	International Conference of Harmonisation Guideline for Good Clinical Practice
PI	Principal Investigator
PN	Practice Nurse
RCT	Randomised Controlled Trial
SDT	Self-determination Theory
TIA	Transient Ischaemic Attack

Declaration

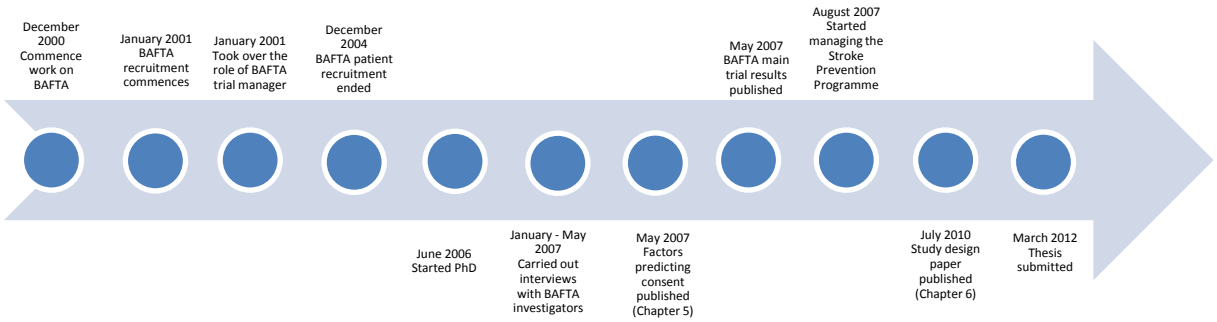
In order to orientate the reader around this thesis, some detail about the author, her involvement in the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) Study, and a timeline to clarify how this thesis fits within that trial is given in this declaration. Clarification of the elements of this thesis carried out by a third party is also included.

I began working on the BAFTA study as a Research Associate in December 2000. My role was to facilitate practice and patient recruitment, to train the investigators who were implementing the trial and to support them throughout the process. In January 2003 I took over the role of Trial Manager for the study. At this point, recruitment was poor, and so a number of protocol and procedural amendments to address the issue were introduced over the next 12 months. BAFTA recruitment ended in December 2004, having exceeded the recruitment target. In 2006 some analysis of BAFTA recruitment data was undertaken (See chapter 5): this was published in 2007. In June 2007 I formally registered to carry out a PhD and undertook interviews with the BAFTA investigators. This task had to be completed by May 2007, because the BAFTA main results were fast tracked for publication and were expected to be published at the end of May. In August 2007 I took over the management of the Stroke Prevention Programme, and continued to work on my PhD alongside this role. In July 2010 a second analysis of BAFTA recruitment data was published (See chapter 6). In March 2012 I submitted the completed thesis, and I continue to manage the Stroke Prevention Programme projects.

All of the statistical analyses were carried out by the author, with the exception of the logistic regression and multi-level modelling in chapter five and the moving F statistic in chapter six.

These were carried out by the BAFTA study statisticians and were done for publication and at the request of peer reviewers. All other work within the thesis was carried out by the author.

Timeline to demonstrate key milestones both in the BAFTA Study and this study



Chapter 1: Introduction

1.1 Structure of the Thesis

This thesis consists of four separate studies which all examine the issue of recruitment of patients to primary care based randomised controlled trials (RCTs). The four studies include:

- A systematic review of the literature pertaining to the recruitment of patients to primary care based RCTs;
- Two separate analyses of recruitment patterns to a large, multi-centred primary care based RCT which examined the optimum way to prevent stroke in older people with atrial fibrillation (AF), the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) Study;
- A qualitative study using semi-structured interviews with general practitioners (GPs) who recruited their patients to BAFTA.

Each study will be presented in a separate chapter. The thesis will start with an overview of the aims and objectives of the project. Chapter two will provide a general background, discussing the literature on the influence of practitioner factors on patient recruitment to RCTs in a variety of settings. Chapter three will present the systematic review of literature specifically pertaining to RCTs in a primary care setting, and will conclude with a description of the BAFTA study.

Chapter four will provide justification for the choice of a mixed methodology approach to the thesis. Chapters five and six will present the two separate analyses of patient recruitment to BAFTA and chapters seven, eight and nine will present the qualitative interview study. The

thesis concludes with an overall discussion of the findings of the studies and recommendations for how to optimise recruitment to primary care based trials.

1.2 Aims and Objectives

The overall aim is to look at practice and/or practitioner factors that influence the recruitment of patients to primary care based RCTs, using BAFTA as a case study. BAFTA is an ideal trial on which to base this analysis for a number of reasons:

- BAFTA was a multi-centred RCT involving a large number of sites located throughout England and Wales. This allows for investigation into the impact of a variety of site factors on recruitment;
- Each site had a separate GP acting as local investigator with responsibility for patient recruitment. This allows for investigation into the impact of a variety of clinician factors on recruitment;
- The trial was initially failing to reach accrual targets, but through the introduction of a number of procedural and protocol amendments managed to enhance the recruitment rate to become ultimately successful. This allows for investigation into changes that may have influenced recruitment.

The main focus of this thesis is practice and/or practitioner factors that impact on patient recruitment. Patient or procedural issues are discussed where they are relevant to clinician considerations. For example, patient perception of trial drugs may influence their decision about participation. However, in this thesis, this would be discussed in the context of how the GP explanation of the trial drugs may influence a patient's attitude to them. It is important to examine the practitioner effect on recruitment because much of the existing literature

considers recruitment from the patient perspective. While important, this may only be part of the story. There is a small but growing body of literature considering practitioner effects which indicates that clinician factors may have a significant influence on a patient's willingness to participate, and is a potentially important aspect of the problems faced by trialists when trying to recruit patients. However, this body of literature is in its infancy, and studies that add to understanding in this area remain vital.

1.3 Specific Objectives

There are five specific objectives for this thesis:

1. To determine what practice or GP factors influence the recruitment of patients to primary care based RCTs, through the identification and assessment of the existing literature pertaining to this issue;
2. To identify whether patient and/or practitioner factors predict the likelihood of a patient giving consent to BAFTA;
3. To identify whether there were any patterns of recruitment to BAFTA that may have been influenced by the protocol or procedural changes that were introduced throughout the course of the trial;
4. To understand the experience of GPs who recruited to BAFTA;
5. To make recommendations for optimal recruitment to trials in primary care, drawing both on the original work described in this thesis, and on the findings of the literature review; and to highlight areas that would benefit from further research.

Chapter 2: General Background

The purpose of this chapter is to set the context in which this study took place. It begins by providing a background to the need for RCTs, explaining their importance to the advancement of health care interventions. The chapter goes on to highlight a significant problem often encountered when conducting RCTs, namely poor patient recruitment, and explains why it is important that this issue is addressed. The chapter will then discuss the general literature search that was carried out to identify the factors that influence recruitment to trials, and how these factors have been addressed.

2.1 Randomised Controlled Trials

Randomised controlled trials are widely accepted as being the best way of evaluating the effects of treatment[1] and health care interventions.[1,2,3] This is because well designed and executed trials are the most appropriate way to minimise bias[4,5] by controlling for both known and unknown confounding factors that may affect outcomes.[5] It is important that an RCT has internal validity (e.g. how was randomisation conducted; was the trial blinded; how was the analysis carried out?) and that its results are clearly presented, clinically relevant and generalisable to an individual clinician's own patient population (e.g. was the trial carried out in primary or secondary care; what were the characteristics of included patients?). It is also important that it has sufficient power to detect any differences between the interventions in question and that adequate numbers of patients enrol. (See Table 1).

Table 1: Key Aspects of the Design of RCTs[6,7]

Feature	**Considerations**
Randomisation of participants	How was the randomisation carried out? Was the allocation schedule concealed from patients and study personnel in advance of study inclusion?
Blinding	Were patients and study personnel blind to the treatment allocation (double blind)? If not, were the outcome assessors blind to the treatment allocation (single blind)?
Trial analysis	Was intention to treat analysis used (maintaining the randomisation by ensuring that groups do not differ systematically)?
Study power	Was a power calculation carried out? Was the sample size large enough to detect differences between trial arms? Were adequate numbers of patients enrolled?
Trial setting	Which country/healthcare system was the trial carried out in? Was it in primary or secondary care? How were participating centres/clinicians recruited?
Study Population	How restrictive were the inclusion/exclusion criteria? What proportions of eligible patients declined randomisation? How were patients identified/diagnosed? What were the baseline clinical characteristics? What was the severity of their disease? What co-morbidities did patients have? Were patients at high risk of complications excluded?

Feature	Considerations
Follow up	How often/long were the follow-ups? How complete was the follow up? Who carried out the follow ups?
Clinical relevance	How does the trial protocol compare with routine practice? What trial interventions were used? What outcome measures were used? How clinically relevant were they? How do the trial patients compare with my patients?

2.2 Recruitment to Randomised Controlled Trials

Regardless of how well designed trials are, their execution is often difficult and fraught with problems. One of the most problematic areas is the enrolment of an adequate number of eligible patients. This is a key success criterion for any trial, as it ensures that sufficient participants are recruited in a reasonable timescale.[8,9] It is also a high level performance criteria on which the research networks will be judged in 2011/12.[10] If a trial fails to recruit to target, it will not meet its power requirement, thus reducing its ability to detect significant effects and resulting in potentially misleading information.[5,11] Slow recruitment may lead to the broadening of inclusion criteria, potentially reducing study validity[12,13] and also causes delays which may affect the generalisability of the study if standard care changes over time.[11] If slow recruitment is due to physician selection of patients, generalisability may be further reduced, as it is possible that only a healthier or more approachable sub-section of the target population is being included[14] (See Table 1). An additional significant problem that arises when studies recruit too slowly is that of cost. Properly conducted RCTs are expensive, and recruitment delays can lead to increased costs.[15,16] Funders may opt to extend the recruitment

period, but they may also decide that the recruitment problems are of such magnitude that the trial should be halted.[4] In a world with limited funding for research, resources spent on failed studies may mean that many important questions may never be adequately addressed, leaving unanswered scientific questions.[15] Despite the importance of adequate recruitment, there is only a limited evidence base on which to base recruitment strategies.[2,4,16] Existing guidance, while useful, is based more on the opinions of experienced researchers than on evidence.[17]

Although it is not easy to quantify the number of trials that experience difficulties, it is estimated that around two thirds never achieve their recruitment targets.[3,18,19] It is likely that how a trial is carried out will influence the success or otherwise of the recruitment. For example, some trials employ researchers to travel to sites to carry out patient recruitment, other trials rely on independent clinicians to enrol patients. Studies with the latter design may be less likely to recruit successfully. One review found that only 12.5% of such studies completed recruitment, even when their timeframe had been extended by 50%.[18] It is possible that, in reality, more trials recruited successfully than is indicated in this paper, because of the problem of publication bias (when reporting trial results, successful trials are more likely to be published; case studies examining recruitment to trials which fail to achieve targets may be more likely to be published than those relating to those recruiting successfully, as the interest is in how to learn from a failure).[18] However, these estimates do give an indication of the potential scale of the problem.

Having established the importance of RCTs and identified that patient recruitment is a major barrier to their successful completion, this chapter will now focus on the existing evidence that addresses this issue, and will ascertain what actions trialists take to improve their recruitment rates.

2.3 General Review of Literature Pertaining to Trial Recruitment

A general literature search was carried out that had two aims:

- Identification of any clinician factors that impact on patient recruitment to RCTs, regardless of disease type or trial setting;
- Identification of interventions that may help to improve recruitment.

The search terms used were:

- Patient recruit* OR accrual OR enrol* AND randomised controlled trial.

Initially the search also included the term OR RCT, but this returned approximately 500,000 hits, most of which were not relevant. No date restrictions were applied, but only studies published in English were included, as the resources needed for translation were not available. As the subject being addressed is very general and is not a narrow clinical question, it was difficult to achieve specificity without losing sensitivity. The Pubmed, Medline and Cochrane databases were searched using the above terms. The titles of all identified papers were looked at, and the abstract of any potentially relevant articles were read; full text was obtained for anything that appeared to be applicable. Papers discussing recruitment to study designs other than RCTs were excluded. Those looking at particularly vulnerable patient groups, for example, children, prisoners or those unable to give informed consent on their own behalf were also excluded. In these cases there are extra requirements for obtaining consent which is likely to add a further layer of complexity to the recruitment issue that is only relevant to studies of this type. Additionally, studies that were confined to looking at recruitment of minority groups were not considered; interventions that are tailored to the particular patient

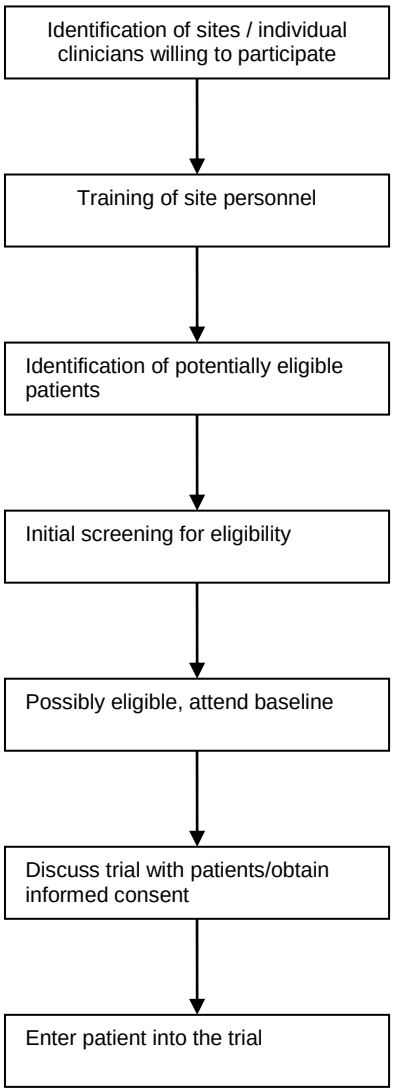
group in question are not likely to be generalisable to less specific populations. Individual papers have not been listed, but will be discussed in relation to the issues they raise.

2.3.1 The Process of Recruiting Patients to RCTs

When looking at the recruitment procedure throughout a trial as a whole, it is apparent that there are a number of phases that need to be carried out before a patient can be successfully enrolled; factors which impact on any of these steps can result in poor recruitment. (See Figure 1, page 10)

The literature identifies a variety of causes of poor recruitment that can potentially affect any point in this process. These can be divided into three main categories: patient orientated factors; clinician orientated factors and practical considerations.[20] (See Table 2, page 14) As the focus of this thesis is on practitioner factors influencing recruitment, patient and practical considerations will be discussed only when they overlap with clinician orientated issues.

Figure 1: Process for Recruitment of Patients to RCTs



Clinician factors and practical considerations can influence both the clinician's decision to participate in a trial (thus impacting upon site recruitment), and once the decision to take part has been made, can affect their ability to recruit patients. Some factors may impact upon both areas. The remainder of this chapter will focus on these two areas.

2.3.2 Influences on Practitioner Willingness to Participate

Identification of sufficient sites and the recruitment of adequate numbers of clinicians are important elements of successful study completion. In fact, a survey of oncologists reported that 76% of responders thought that the reluctance of clinicians to participate was a greater barrier to successful trial completion than the reluctance of patients.[21] An understanding of what motivates clinicians to take part in a trial, or what barriers they face when making that decision, may help trialists to ensure that they can maximise site recruitment.

2.3.2.1 Factors that Promote Participation

The literature cites a number of reasons why physicians are motivated to participate in trials. These are summarised in table two (Page 13).

Interest in the study question

Interest and enthusiasm for the study question is something that clinicians will take into account when considering trial participation. A survey of physicians who were recruiting patients to a hypertension trial found that 34% of them stated that interest in the agents being compared in the study was an important factor in their decision to take part,[22] while 17% of surveyed oncologists felt that scientifically uninteresting questions would deter them from participation.[23] In order to encourage participation, the question also needs to have an important scientific aim,[4,16,24,25,26,27] and should be relevant to their clinical practice (conditions that they see regularly would be especially relevant).[28] GPs for example, are less likely to be involved in cancer treatment trials, as these patients are usually cared for in a specialist setting.

This is a difficult area in which to make changes that could have an impact on clinician participation rates; a trial is funded to look at a specific question and practitioners will either be interested in it or they will not. It may be that different ways of approaching clinicians to participate influences their perception of the study question, although there are few studies looking at whether this is the case. Ward et al reported that 78% of clinicians were encouraged to take part to some extent by having a telephone call from the chief investigator prior to receiving an invitation letter,[29] so it is possible that how the initial approach is carried out could affect clinician participation rates. The literature also advises trialists to place emphasis on the benefits, both to the clinician and to future patients, of their involvement.[15,30] However, this advice is based on anecdotal evidence, and there are no studies that have tested whether this is the case, and if so, the optimum way of achieving this.

Ability to carry out the study

An ability to actually carry out the work involved in participation is also a prime consideration of clinicians contemplating involvement. Many centres will not agree to take part if they feel that they do not have adequate numbers of staff. A study of reasons for declining participation in a trial looking at modes of delivery for pre-term breech babies found almost 50% of non-participating centres cited insufficient staff to obtain properly informed consent as a major barrier.[31] Furthermore, the time commitment necessary for trial involvement deters some. A survey of research active clinicians found that for 83%, time available to them to undertake the extra duties associated with trials was a major barrier to their participation.[32] Trialists are advised to minimise workload and to keep the protocol and data collection forms as simple as possible in order to encourage involvement.[17] Although this

is intuitive advice, there is no clear evidence that simplicity or minimisation of workload actually improves clinician recruitment.

Table 2: Clinician Reasons for Participating in an RCT

Interest in the study question
➢ Scientifically interesting question ➢ Interest in the agents under investigation ➢ Relevance to clinical practice
Ability to carry out the study
➢ Time constraints ➢ Adequate numbers of suitably trained staff
Other reasons for participation
➢ Participation of an academic research group or clinical research organisation ➢ Personal relationships o Personal acquaintance with the researchers o Colleague who agreed to participate ➢ Personal appeal by the research team ➢ Professional obligation ➢ Corporate decision to participate

Other reasons for participation

A number of other motivators to participate were cited in the literature. These included: professional or personal relationships with the researchers or other participating colleagues;[33] personal appeal by the research team;[34] professional obligation;[34] or involvement of an academic research group.[34] However, these findings all came from surveys of clinicians who participated in trials. They were asked to indicate which factors influenced their decision, or to rank them in order of their perceived importance. It is not clear from the articles how the questionnaires were designed, so it is possible that these factors are assumed by researchers to be important, but are not actually relevant in practice. Not all participating clinicians express interest in the study. Some are involved purely because a corporate decision by the Trust to take part has been made.[35]

2.3.3 Clinician Factors that Influence Patient Recruitment

This section will look at clinician factors that may impact on their ability to recruit patients.

2.3.3.1 Impact of Clinician Motivation to Participate on Patient Recruitment Rates

Having examined the different considerations that play a part in the decision to participate, the relative importance of each factor is not clear. It may be, for example, that a clinician may not express an interest in the question, but feels strongly enough about their professional obligation that they will still agree to participation. Simple involvement, however, does not necessarily lead to good patient recruitment. Csimma et al stated that an enthusiastic lead investigator at each site was the most important factor associated with recruitment, although no detail was given about how they came to this conclusion.[36] It remains unclear what makes some physicians enrol more patients than others. If it were possible to identify this, then it

may be possible for trialists to target their practitioner recruitment efforts at those clinicians most likely to recruit successfully.

A number of studies have looked at whether a physician's reasons for participation influences their ability to recruit successfully, and these have been summarised in a Cochrane Review of incentives and disincentives to clinician participation.[35] This review found three studies that considered whether there was an association between factors that motivated clinicians to participate, and their subsequent recruitment activity.[33,34,37] All three studies were postal surveys of physicians who had recruited to an RCT, asking them what motivated them to participate, or to rank a number of factors in order of their perceived importance. The results of these studies are equivocal. There was an association with better patient recruitment for those ranking involvement of an academic research group highly against those who did not (adjusted OR 2.9, 95% CI 1.2-6.9),[34] whereas, for clinicians who became involved because of professional relationships with the researchers or other participating colleagues, there was a higher percentage who recruited no patients when compared with clinicians who cited other motivations to participate (50% versus 15.5%).[33] There was also a negative association with patient recruitment for those who ranked personal appeal by the research team as an important motivator (OR 0.4, 95% CI 0.2-0.9).[34] There was no association with recruitment for those who ranked professional obligation as important (OR 1.7, 95% CI 0.7-3.7).[34] This evidence is slightly at odds with the current advice; involvement of a local 'champion' in a trial, with the aim of encouraging clinician participation is an approach that is recommended.[17] These findings point to the fact that, while this advice may increase the number of doctors willing to take part, using personal appeals or contacts may ultimately result in the participation of clinicians that are poor recruiters of study patients.

Interest in the specific study question was also found to have no association with recruitment (OR 1.0, 95% CI 0.5-2.2),[34] which may mean that those without an interest will opt to not participate rather than agree but fail to recruit. However, those expressing an interest in learning about research per se, were found to have a positive association with recruitment (74.8% of recruiters cited interest in learning about research versus 63.8% of non-recruiters, $p<0.02$).[37] It may, therefore, be worthwhile for researchers to identify how to 'sell' their trial in such a way as to maximise interest amongst clinicians, or to identify those doctors who are interested enough in research to participate despite having little interest in the topic area.

For some clinicians, regardless of their reasons for taking part, the study question may raise issues further down the recruitment stream: some factors will have an influence at more than one point. As discussed, clinician agreement to participate does not ensure that they will successfully recruit adequate numbers of patients. The same factors that deter some from participation may not deter others, and their concerns may only come to light when actively recruiting patients. This is demonstrated by the many trials that highlight discrepancies between the number of practitioners who agree to participate and the number of those who actually recruit.[14,35]

2.3.3.2 Other Clinician Factors that may Impact on Patient Recruitment Rates

Once they have agreed to enrol their patients into a trial, clinicians need to identify and approach their eligible patients, and carry out the informed consent process with each one before they can be included in the study. (See Figure 1, page 10) There are many factors that can affect any point in the process (See Table 3, page 18) and result in poor recruitment. Each factor will now be considered in turn.

2.3.3.2.1 Ethical Considerations of RCTs

All studies carried out in the United Kingdom are required to have prior approval from a designated Ethics Committee, and to conform to the standards of Good Clinical Practice (GCP) as laid down by the International Conference of Harmonisation Guideline for Good Clinical Practice (ICHGCP).[38] This guidance has its origins in the Declaration of Helsinki (1964) and its aim is to safeguard the safety and well-being of any human subject. Prior to any patient being approached, ethics committees look at all aspects of a trial to ensure that it is not likely to cause undue harm. They consider the treatments in question and whether there is an imbalance of risks between the treatment arms on offer; whether there is a genuine clinical question that has not already been answered, thus justifying the exposure of patients to potential risk; and aspects of the informed consent process, including who will be obtaining consent and what is included in the patient information sheet. There are two central ethical tenets to RCTs that can influence recruitment: clinical equipoise and fully informed consent.

Clinical Equipoise

Clinical equipoise provides the ethical basis for all randomised trials involving humans, and means that there is genuine medical uncertainty as to which treatment is best. In addition, clinicians who recruit patients to trials also need to consider the ethics of the trial in relation to their own personal viewpoint. They need to be happy with all of the treatments on offer as part of the study and, for each individual patient that they enrol they need to be in equipoise:[39] this is known as personal equipoise. Ethical concerns may arise when investigators begin to favour one treatment arm over another, and where this is the case, they should not be offering trial entry to their patients. Even if the clinician is in equipoise over the aim of the study, for

patients where they are not in personal equipoise, they should treat as they feel most appropriate and not consider them eligible for the trial.

Table 3: Clinician Factors that Impact on Accrual

Ethical Considerations
➢ Equipoise ➢ Informed Consent o Process of obtaining informed consent
Impact on the doctor/patient relationship
➢ Discussion of uncertainty ➢ Dual role of physician and researcher ➢ Loss of clinical autonomy
Structural barriers
➢ Time constraints ➢ Staff shortages ➢ Research experience and training

Despite agreeing to take part, some clinicians express concerns about disparities between the treatment arms or find that they prefer one of the treatments over the other[14] and this may impact on their ability to recruit. Those who have a strong preference may not recruit as many of their eligible patients as those who have none,[4,24] although whether or not this is the case remains unclear: de Witt et al's survey of participating clinicians, found no differences in recruitment according to views about trial interventions (OR 1.0, 95% CI 0.5-2.2).[34] Concerns

about treatment arms can depend upon whether there is a big divergence between them. In trials where the balance of risk is not distributed evenly across both arms, clinicians become less comfortable with involving their patients.[26] For example, including a placebo arm in a trial can have a detrimental impact on recruitment: 37% of surveyed oncologists would recruit to a trial with a placebo arm versus 68% who would recruit to a trial with two active treatments.[40] Conversely, the authors of an observational study of interactions between patients and oncologists concluded that there was a reluctance to recruit patients with a poor prognosis to a trial in which they may be randomised to a standard treatment; they would rather choose to give the patient the non-standard treatment.[41]

This situation begs the question, why do clinicians agree to participate if they are not in clinical equipoise about the study treatments? It may be that, while they are happy with the trial in principle, they find it more difficult when actually faced with making the choices with regard to one of their patients, and concerns about treatments come to the fore.[35] While they are actually in clinical equipoise over the study question, they may not be in personal equipoise with individual patients, and so are selective about whom they consider for trial entry.

This may also influence how they discuss the trial with their patients. One study that audio recorded trial discussions found that most clinicians presented general uncertainty about the treatment options.[42] Some clinicians, as well as communicating their clinical equipoise, were also explicit about personal equipoise and explained that they were happy with:

> *Either arm of treatment to (name of child) … if I wasn't I'd be giving you the one that I thought was better* [42] *(p6)*

Byrne-Davis et al demonstrate that clinicians discuss the trial with their patients in different ways. They describe how some clinicians distance themselves from the trial, by contrasting between the trial perspective (e.g. they're looking to see if the leukaemia is above a certain level) and the clinical team's perspective (e.g. from our point of view s/he is in remission), while others use pronouns that imply they are allied with the trial (e.g. we're running a trial).[42] It has previously been demonstrated that the order in which information about trial treatment arms is given[43] and patient acceptance of equipoise[44] both impact upon patient willingness to participate; how clinicians communicate with their patients is therefore likely to influence patient understanding and acceptance of trial concepts. Given this, it would be useful to determine whether the kind of communication differences highlighted by Byrne-Davis et al resulted in differential recruitment rates between recruiters. Unfortunately, this was not reported[42] and the full impact of equipoise on recruitment remains unknown.

Informed Consent

Although ICHGCP covers all aspects of how a trial is run, one of the central tenets of GCP is the process of gaining fully informed consent from any person who may be offered entry to a research study. GCP details six main requirements that need to be fulfilled before it can be assumed that fully informed consent has been given. These are:

- Prior written approval from a medical ethics committee of the written consent form and any other written information to be provided to a subject;
- Subjects must not be coerced or unduly influenced to participate;
- The investigator should fully inform the subject of all pertinent aspects of the trial. There are 21 points that need to be conveyed to the subject. (See Table 4, page 21);

- Language used, both written and oral, should be as non-technical as possible and should be understandable by the subject;
- Subject should be given ample time to decide whether or not to participate and be given the opportunity to have any questions they may have answered;
- The written informed consent form should be signed and dated by both the investigator and the subject prior to trial entry. A copy of this should be given to the subject.

Practical aspects for obtaining informed consent need to be considered during the protocol design phase. They need to balance the requirements of GCP and pragmatic considerations relating to how patients are identified and approached. The minutiae are likely to be study specific. However, most trials would aim to include as many of the GCP required points as possible in the patient information sheet, and follow this up with a study appointment with the recruiter who will address any concerns or queries that the patient may have. Trials where patients are recruited during routine consultations need to carefully consider how they will fulfil the requirement for giving subjects adequate time to make their decision.

Table 4: Areas to be Explained During the Informed Consent Procedure[38]

➢ The trial involves research
➢ The purpose of the trial
➢ The trial treatment (s) and the probability for random assignment for each treatment
➢ The trial procedures to be followed, including all invasive procedures
➢ The subject's responsibilities

- Those aspects of the trial that are experimental
- The reasonably foreseeable risks or inconveniences to the subject
- The reasonable expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this
- The alternative procedure(s) or course(s) of treatment that may be available, and their important benefits and risks
- The compensation and/or treatment available in the event of a trial related injury
- The anticipated payment, if any, to the subject for trial participation
- The anticipated expenses, if any, to the subject for trial participation
- That the subjects involvement in the trial is voluntary and that they may refuse trial entry, or withdraw at any time without any penalty or impact on their medical care
- That regulatory authorities will have access to the subject's original medical records for verification of trial procedures
- Records identifying the subject will be kept confidential. If trial results are published the individual's identity will remain confidential
- The subject will be informed if information becomes available that may be relevant to their willingness to continue participation
- The person to contact for further information about the trial and whom to contact in the event of a trial related injury
- The foreseeable circumstances under which the subject's participation may be terminated
- The expected duration of their participation
- The approximate number of subjects involved in the trial

The process of obtaining fully informed consent from patients has often been cited as a barrier to accrual, and was listed as one of the five most difficult areas of discussion during the oncology consultation.[45] It has been identified by physicians as a reason for failing, or for making it difficult, to recruit patients;[4] There is a significant body of literature that examines informed consent from the patient perspective. Much of this focuses on patient understanding of the trial, and whether they fully appreciate what they have consented to. Although the literature produces some mixed evidence, the general consensus is that patients have a poor understanding of trials, often do not understand the reason for randomisation and experience the 'therapeutic misconception' (the belief that their doctor has chosen the best treatment for them).[46] It would be logical to assume that improved understanding of trial concepts would result in an increased number of people willing to participate. However, it seems that this may not be the case. One study tested two different methods of information giving: 'passive' receipt of information via brochures; and interactive information receipt via computer. The mean understanding score for agreers and refusers were calculated. They found that improved understanding of trials seems to have had a detrimental effect on willingness to consent (mean understanding score, agreers 13.19, refusers 14.06, p=0.03).[47] Another study randomised patients to receive standard trial entry invitation, or to receive standard invitation plus a questionnaire about their medical condition. They found that people receiving the questionnaire were more likely to participate (RR1.37, 95% CI 1.13-1.65) and concluded that increased awareness about their condition could have been responsible for the increased willingness to participate.[48] While it is vital to ensure that a patient understands and accepts what they are agreeing to when considering trial participation, it may be that placing greater emphasis on the understanding of their medical condition during the consent process would be beneficial to recruitment rates.

It is probable that how trials are discussed with patients can have an influence on their willingness to enrol. One qualitative interview project demonstrated that the order in which the treatment arms of a trial for prostate cancer were explained influenced the recruitment rate; re-ordering the presentation of treatment options contributed to the increase in recruitment rates from 40% to 70%.[43] A Cochrane review of strategies to improve recruitment to RCTs examined 27 studies that evaluated the effects of nine different categories of recruitment interventions. Eighteen of these studies modified how information was given to potential participants, including: amended information sheets; video information versus written information or use of interactive computer programmes to present trial information.[49] None of the studies in this Cochrane review provided conclusive evidence that the modifications to the way information is given improved accrual, although the use of an interactive computer programme to present trial information 'probably slightly' improved recruitment to a hypothetical cancer trial when compared with an audio tape presentation (RR 1.48, 95% CI 1.00-2.18).[47,49]

The literature often focuses on the need to determine patient levels of understanding to ensure that patients have given fully informed consent. Whilst it is imperative that people are fully informed before they give consent to participation, consideration also needs to be given to ensuring that patients also give fully informed refusal, as those who do not understand the process may be those who do not wish to take part.[46] It could be argued that patients should be given the information in such a way that those who decline participation have made as much of an informed decision as those who accept, rather than refusing consent because they have not understood the trial or have not received the information that they need. This is an important issue if researchers are to achieve their targets whilst ensuring that the right patients both enter and decline trial participation. If it is true that how a clinician discusses the trial

with a patient influences their decision to participate, consideration of factors that impact on this process is important.

Factors influencing the informed consent discussion

The appropriateness of the informed consent process has been questioned by a number of clinicians. 40% of oncologists who enrol patients onto trials believe that consent is not designed to protect patients.[4,16,50] Surgeons in one study felt that obtaining informed consent was an arduous process, stating that, while they may 'vigorously support' the trial, they cannot bring themselves to ask their patients to sign up: '*I look at the informed consent sheet which is far in excess of what is appropriate and that's it*.[51 (p1365)] If there was not the need for written informed consent, 87% of 484 surveyed clinicians stated that they would enter more patients in trials.[4,52]

Investigators were often uncomfortable with some aspects of the informed consent consultation; one of the reasons given is that they were not comfortable explaining trials to their patients,[41] and some were too embarrassed to introduce the subject with their patients.[37] Many clinicians are uncomfortable with admitting to uncertainty, a central aspect of the consent process (discussed in detail in section 2.3.3.2.2). Many other reasons for having problems with consent have also been cited. 38% of surgeons recruiting to a cancer trial said that they had trouble with the informed consent process, specifically, the need to disclose information to patients that they would usually discuss as part of the usual consultation in a more flexible manner. Respondents appeared concerned that the informed consent form regulates formerly flexible decisions.[53] Clinicians often found it difficult to initiate the clinical trial discussion,[45] or to assess the level of information that patients want to be given.[52] They

worried that too much information may frighten patients[31] or even lead to increased morbidity or mortality.[52]

In addition to these general concerns about the consent discussion, many cite difficulties with discussion of the specific terms used as part of a trial, for example, randomisation or placebo.[54] Recruiters often feel ill prepared for carrying out consent and feel that they do not have adequate training or skills for the role.[4] These concerns may lead to sub-optimum patient recruitment, encouraging clinicians to select the patients that they feel best able to communicate with. The literature recommends that clinicians consider that they will need to explain these terms, but there is little that discusses how this would be best achieved.

Despite the wealth of literature examining informed consent, and the assumption that it impacts negatively on patient recruitment, there is no clear evidence about whether this is actually the case. The evidence rarely links clinician feelings about consent, or how they conduct the process to recruitment rates. Three survey studies did try to link these factors, but their findings were inconclusive. For example, one small survey of 40 oncologists found no significant difference in referral rates between those comfortable with explaining trials and those who were not, but potentially important differences could not be excluded given the small sample size (OR 5.05, 95% CI 0.85-29.91).[55] Another study reported that there was a significant difference in recruitment between oncologists that have, and oncologists who do not have issues with obtaining informed consent (0% of those reaching recruitment targets cited problems with consent versus 37% of those who did not reach targets, $p<0.005$).[52] Conversely, a higher proportion of GPs who said that they were 'too embarrassed' to initiate trial discussions recruited than those who were not embarrassed (39.5% versus 22.7%, $p<0.02$).[37] This finding seems counter-intuitive, and the authors offer no explanation for this

result. It may be that clinicians from different specialities have different concerns about consent, for example, oncologists and GPs, and that this accounts for the conflicting evidence. However, these findings do highlight the continued uncertainty around the subject.

2.3.3.2.2 Impact on the Doctor/Patient Relationship

In addition to the factors already discussed, a number of other issues have been identified that exacerbate the recruitment problem. Clinician concerns about the impact of trial inclusion on the doctor/patient relationship have a negative impact on recruitment,[26,35] and may influence clinicians to select which patients they approach about participation. A systematic review of factors that limit the progress of RCTs found that, out of 84 primary research papers (qualitative and quantitative) reporting findings related to the recruitment of clinicians or patients, 12 discussed how the doctor/patient relationship may have acted as a barrier to recruitment.[4] There are a number of possible reasons for this (See Table 3, page 18) and these will now be considered in turn.

Discussion of uncertainty

Studies of the doctor/patient relationship indicate that the main drivers of the relationship are patient's trust in the doctor's expert knowledge, individualised decision making power and a belief that a doctor will do their best for an individual patient.[56] A concern is that the discussion of uncertainty disrupts that dynamic and has a negative impact on the relationship.[25,52] The change in image from confident clinician to one with an attitude of uncertainty raises instinctive resistance amongst clinicians.[27] Many are concerned that this would necessitate a major shift in the usual doctor/patient interaction and that patient morale may be reduced if they were exposed to the implicit indecision of a trial.[50,52] In an interview study, many clinicians cited concerns with the need to admit uncertainty, typically saying:

> *For the trial, I guess I'll have to start to learn to say 'I don't know which is best.' I'm not sure I will be very comfortable doing that for too long.*[56 (p220)]

In one survey, this worry was found to have a negative impact on recruitment.[57] Richardson et al found that those expressing difficulties with recruitment consultations were less likely to have recruited than those who did not (90 participants, $p= 0.04$). Another survey supported this finding. They reported that none of the 25 surgeons who recruited to target cited concerns with the discussion of uncertainty, while eight out of 32 who failed to recruit any patients perceived it as a problem ($p<0.025$).[51]

Dual role of physician and researcher

Another factor that leads to concerns about the doctor/patient relationship is the difficulty faced by clinicians when they are trying to fulfil the dual role of physician and researcher.[4,41] A traditional characteristic of the medical profession is its high social status, which is mainly derived from patients' trust in their doctor's knowledge and skills.[56] When faced with a clinician's uncertainty, the shift in this perception results in conflict between the roles of researcher and clinician.[15] A clinician's main priority is the well-being of patients. However, participation in a trial brings a competing priority, that of advancing scientific knowledge, and there is a perceived difficulty in balancing these two aims. Most focus more on fulfilling their patient needs than offering patients the opportunity to take part in research.[15] This conflict can lead to the situation where, despite agreeing with the trial in principle, there is a subsequent failure to enrol patients.[31]

Clinical autonomy

The final consideration that may impact on the doctor/patient relationship is the potential loss of clinical autonomy. Clinicians are reluctant to relinquish the power to make individual decisions about their patients;[14,52,53,56] 82% of clinicians cited this loss of independence as a barrier to recruitment.[14] Clinicians also did not like the loss of flexibility implicit with following a study protocol [51,52,56] and wanted to retain the ability to act on their clinical judgement even where it conflicted with published data.[53] Concerns about this loss of autonomy seem to have a negative impact on recruitment, as doctors select which patients they approach about the trial.[4] However, despite the fact that this is often reported to be a barrier to recruitment, it must be noted that much of the evidence for this comes from one main author, and each project uses similar methodology, namely surveys of physicians recruiting to oncology trials.[14,51,52,53,56] Prior assumptions of the authors that loss of autonomy is a barrier to recruitment may have influenced the questions asked, and therefore shaped the findings. Details of questions asked were also not given. Caution, therefore, must be applied to this conclusion.

Logically it would be expected that concerns about the doctor/patient relationship would have a negative impact on accrual. As discussed, the evidence is mixed, with contradictory findings and no RCTs that test the theory. However, these areas have the potential to impact on many of the recruitment steps. They may influence the decision whether or not to participate, affect which patients are selected for trial entry, alter the informed consent discussion and create concerns about the generalisability of the study.

2.3.3.2.3 Structural Barriers to Recruitment

Time constraints

Even after a clinician has agreed to participate, the time it takes to enrol and follow up trial patients may still be a significant barrier to accrual.[16] Time spent on research often has to sit within usual clinical practice and many clinicians do not have adequate time within the constraints of their current workloads to enrol patients into trials. The time demands of patient identification and obtaining consent are cited as particular barriers.[16,58] These problems are exacerbated by complex protocols and poorly designed data collection forms. Trialists need to consider ways of providing appropriate support to clinicians to ensure lack of time will not deter them from taking part or inhibit their ability to carry out study procedures.[4] One way is to ensure that trial processes are as streamlined as possible; paperwork should be succinct and uncomplicated, and identification of potential patients should be straightforward.[17] Once again the advice, whilst intuitive, is not based on evidence. In fact, the evidence about whether time constraints adversely affect accrual is mixed. Oncologists who consider that 'trials involve extra work' were more likely to have recruited than those who did not (OR 92.94, 95% CI 4.54-1902.11), but those that thought paperwork time consuming were less likely to have done (OR 0.0011, 95% CI 0.00002-0.06): recruitment by surgeons was not affected by their views on the practical aspects of a trial.[55]

Staff Shortages

The lack of support staff is also cited as a barrier to trial recruitment.[4,35] Some sites will not participate if they feel that they do not have enough staff to enable them to take fully informed consent[4] whereas other sites may participate, but leave the majority of the work to be carried out by the recruiting doctor. Lack of support staff, (i.e. research nurses), may have a

detrimental impact on patient recruitment, although again the evidence is not clear cut. For example, GPs who had assistance with a trial from a practice nurse were found to be more likely to recruit than those recruiting alone (56% of GPs who had help from a nurse recruited versus 33% of GPs who recruited alone, p=0.02).[57] On the other hand, there were no significant differences in recruitment between oncologists who had support staff, and those who did not, though the study was not powered to exclude a possible effect (OR 4.99, 95% CI 0.64 – 38.63).[55] Some trials have sufficient funding to allow researchers to 'parachute' into sites to carry out study tasks, thus minimising work for clinicians. This may help to overcome the barriers caused by time constraints. An examination of site factors affecting recruitment to the Cardiac Arrhythmia Suppression Trial (CAST) found a positive correlation between accrual and the availability of CAST nurse clinicians on site. Recruitment was better where there were more full time equivalent CAST nurses on site and where they were involved in fewer competing trials.[59] Unfortunately it was unclear from the published report whether the nurses were employed by CAST and sent to sites to recruit, or whether they were nurses who worked on site anyway and were devoting some of their time to the trial. Although this example adds weight to the argument that increased support for investigators leads to improved recruitment, prospective studies examining this area could determine the optimum way that support with staffing could maximise recruitment.

Research Experience and Training

Prescott et al, in their systematic review of factors that limit the progress of RCTs, found 12 studies that highlighted problems encountered with the lack of trained staff.[4] Five of these found that clinicians were often inadequately prepared for the role;[14,27,32,52,56] that training is often inadequate[59] and that there is a perception amongst clinicians that there is a diminished number and calibre of researchers due to reduced career opportunities.[32] Taylor et al suggest

that physicians need to be better educated on the rationale of RCTs in order to improve accrual.[56] It would seem logical that better understanding of trials on behalf of recruiters would translate into better explanation of studies, reduced patient selection, and therefore, improved recruitment.

Recruiters also need to be well informed about the aims of any study they are involved with, and to have a good understanding of the treatment arms and study processes.[60] This is highlighted by the findings of a failed study looking at an intervention to enable people with mental health issues to return to work. Interviews were conducted with recruiters to determine why patient accrual was so poor. They found that recruiters, despite having received instruction about the study protocol, had a poor understanding of both general RCT tenets, including randomisation and equipoise, and a lack of knowledge about the study protocol. Many recruiters were confused about the treatment arms, and felt that the control arm was no treatment at all. In fact, the control arm was standard practice. This confusion communicated itself to the patients, and they in turn refused trial participation.[15]

Three articles state that lack of research experience on behalf of the investigator is also a barrier to recruitment,[32,61,62] but not all studies came to the same conclusion. De Witt et al found that prior research experience had no association with recruitment rates (OR 1.5, 95% CI 0.6-3.6).[34] In the United Kingdom, research networks are now used to identify sites that are suitable for recruiting patients to trials. They ensure that clinicians are well prepared to carry out research, offering training and support for research processes and ensuring that sites are able to carry out all study procedures.[63] However, anecdotally, it seems that some research networks place emphasis on larger sites, and prioritise sites that are research experienced for involvement in trials. While this approach may reduce generic training requirements (e.g.

GCP), paradoxically it may have a detrimental effect on recruitment. Investigators that have no prior experience of research may recruit as well as, or better than, those who have had involvement with other trials, as prior research experience has not been shown to be associated with recruitment.[34]

2.3.4 Problems with the Existing Evidence

There are a number of limitations to the current literature. Many of the publications are 10 years old or more and there have been significant changes to how trials are conducted since this time, especially with regard to informed consent, so it is not clear how relevant the findings remain. Many articles are observational or descriptive studies of individual projects, and do not relate their findings to recruitment rates. While they provide a useful insight into the subject, they do not provide any evidence that their procedures were linked to their recruitment. No articles were found that examined recruitment to a trial that was failing to recruit patients but which introduced changes that improved accrual, which might provide useful insight into strategies that may work.[2] A large number of studies are surveys of recruiting clinicians and as such they may suffer from biases inherent in such study designs. Surveys are cross sectional studies, generally carried out at one point in time, and as such provide a snapshot of a situation and give no indication of the sequence of events under investigation. Therefore, they can imply association but cannot determine whether the outcome is as a result of the exposure.[64] Furthermore, surveys can suffer from bias, for example non-response bias, where a low response rate is obtained. This is especially problematic where responders differ systematically from non-responders. They may also suffer from recall bias, where respondents can be misclassified during analysis due to an error in their memory of the situation under question.[64] Few RCTs were found that actually tested any interventions to improve recruitment, and although a few studies have found various

factors that are associated with recruitment rates, there were none that looked at potential interventions to overcome the issue. Furthermore, the evidence that is available is often conflicting, which may be due to specific features (for example, the impact of inclusion/exclusion criteria) of the individual trials.

Another major limitation of the literature is the fact that many of the papers relate to secondary care based cancer trials, and as such, may have issues specific to their setting or disease area. For trialists looking to carry out RCTs in a primary care setting, the relevance of this evidence is unclear. Therefore, the next chapter will look specifically at the evidence relating to primary care based RCTs to establish how far the factors already identified remain relevant when recruiting to trials in this setting.

Chapter 3: Review of Literature Pertaining to Primary Care Based RCTs

As discussed in section 2.1, it is important for external validity that trials are carried out in an appropriate setting. For GPs to be willing to rely on the evidence from trials, they need to be sure that it is relevant for their patients. Therefore, GPs are looking for evidence from trials carried out in a primary care setting. As discussed, one of the problems with the literature is that much of it relates to issues of recruitment to secondary care based cancer trials: there seems to be little discussion about RCTs carried out in the primary care setting. While some of the issues may be generic, it is likely that there are a different set of considerations to take into account. In primary care, for example, the nature of the disease being studied is likely to be different: clinicians may find it less difficult to introduce the concept of randomisation when they are not discussing a potentially terminal illness such as cancer.

For trials carried out in a primary care setting, the steps leading to patient recruitment are likely to be identical (See Figure 1, page 10) and some of the central issues (for example, clinical equipoise and the need to follow GCP guidance on obtaining informed consent) will remain the same as those described in section 2.3.3.2. However, it is possible that the factors that affect these steps in primary care based trials differ from those in other settings. Primary care based trials, for example, often involve higher numbers of smaller sites than are needed when carrying out hospital based studies. These sites are often very diverse, both geographically and in their structure, and may have very different population mixes or disease types to those found in secondary care: all of these considerations could mean that recruitment problems at any step in the process are magnified in primary care based studies.

This chapter will look at the literature pertaining to primary care based trials, determine whether or not the issues that have already been identified remain relevant when specifically considering trials in this setting, and whether there are any issues that apply only to these studies. Interventions to overcome any issues raised will also be discussed.

A review of the literature was carried out that had two objectives:

- To determine how far the recruitment issues that have already been identified apply to RCTs carried out in a primary care setting;
- To identify interventions that impact on recruitment to primary care based RCTs

One of the problems when carrying out searches for methodological papers is that it is not a clearly defined clinical question that is being asked, and as such it is difficult to narrow the search down without losing too many relevant articles.[4] The search strategies employed here aimed to maximise the number of relevant articles while keeping the numbers of papers to manageable levels.

3.1 Methods

The Pubmed and Pubmed Central (PMC) databases were searched, as was the Cochrane Library. The searches run in the Pubmed database allowed simultaneous searching of Pubmed, Medline and PMC. These databases were selected as it was felt that many of the relevant articles would be identified through them. The Cochrane database was included to identify any Cochrane Reviews that may be relevant to the question. As it is not possible to conduct very sensitive searches for such a non-specific question, the databases of two journals were also searched (Trials and Biomed Central Methodology) in order to identify any further articles that had not been picked up through the initial searches. Finally, the reference lists of

all relevant studies were examined to try to ensure that no important papers had been overlooked.

3.1.1 Search Criteria

The search criteria chosen aimed to cover the commonly used terms both for patient recruitment and primary care; similar terms have been used in prior reviews[4,35,11] (See Table 5). Initially the Pubmed and PMC databases were searched with RCT as RCT*: this approach returned 640,000 references, so the wild card was removed and the search re-run. This reduced the number of papers returned to more manageable levels, hopefully without removing any of relevance. Date ranges were applied to the searches, with publications prior to 1990 being excluded. It was felt that those prior to 1990 may not be relevant to current practice as many changes both to general practice and approaches towards the conduct of research had taken place since that time. The searches were carried out in March 2011, so articles published post March were also not included.

Table 5: Search Criteria

Database	Search Criteria	Restrictions
Pubmed	Random* control* trial OR RCT AND primary care OR family practice OR GP OR family physician OR community AND recruit* OR accru* OR enrol*	English papers Articles with abstracts Humans From 1990 – March week 1 2011.
Pubmed Central	Random* control* trial OR RCT AND primary care OR family practice OR GP OR family physician OR community AND recruit* OR accru* OR enrol*	English papers Articles with abstracts Humans From 1990 – March week 1 2011.
Cochrane	recruitment AND "random and trial" AND "consent or accrual" and "primary care"	None
Trials	Random* control* trial AND primary care AND recruit*.	None
BMC Methodology	Random* control* trial AND primary care AND recruit*.	None

The criteria used across different databases were kept as similar as possible. The process of building searches differs between databases: those run on the Cochrane and the individual journal databases were less flexible than Pubmed and PMC, and there was less scope for including alternative terms for primary care or recruitment.

3.1.2 Selection Criteria

Papers were eligible if there was discussion of the practice or practitioner issues influencing patient recruitment, although articles not available in English were excluded as there were no resources available to carry out translation. Papers were also excluded if they looked only at the recruitment of potentially vulnerable patient groups, for example, children or prisoners, as there are likely to be specific issues with recruiting these populations that are not relevant to primary care based trials in general. Similarly, those restricted to the recruitment of ethnic minority populations were excluded. Finally, papers discussing the recruitment of patients to studies with designs other than individually randomised RCTs were not considered.

3.1.3 Quality Assessment

No formal assessment of the quality of included articles was carried out, for two reasons:

- The aim of the review was to determine whether the factors found to influence recruitment to trials in general were relevant to those carried out in primary care so any relevant articles were considered regardless of their methodology
- Very few trials of recruitment processes have been carried out, and none of these were specific to primary care

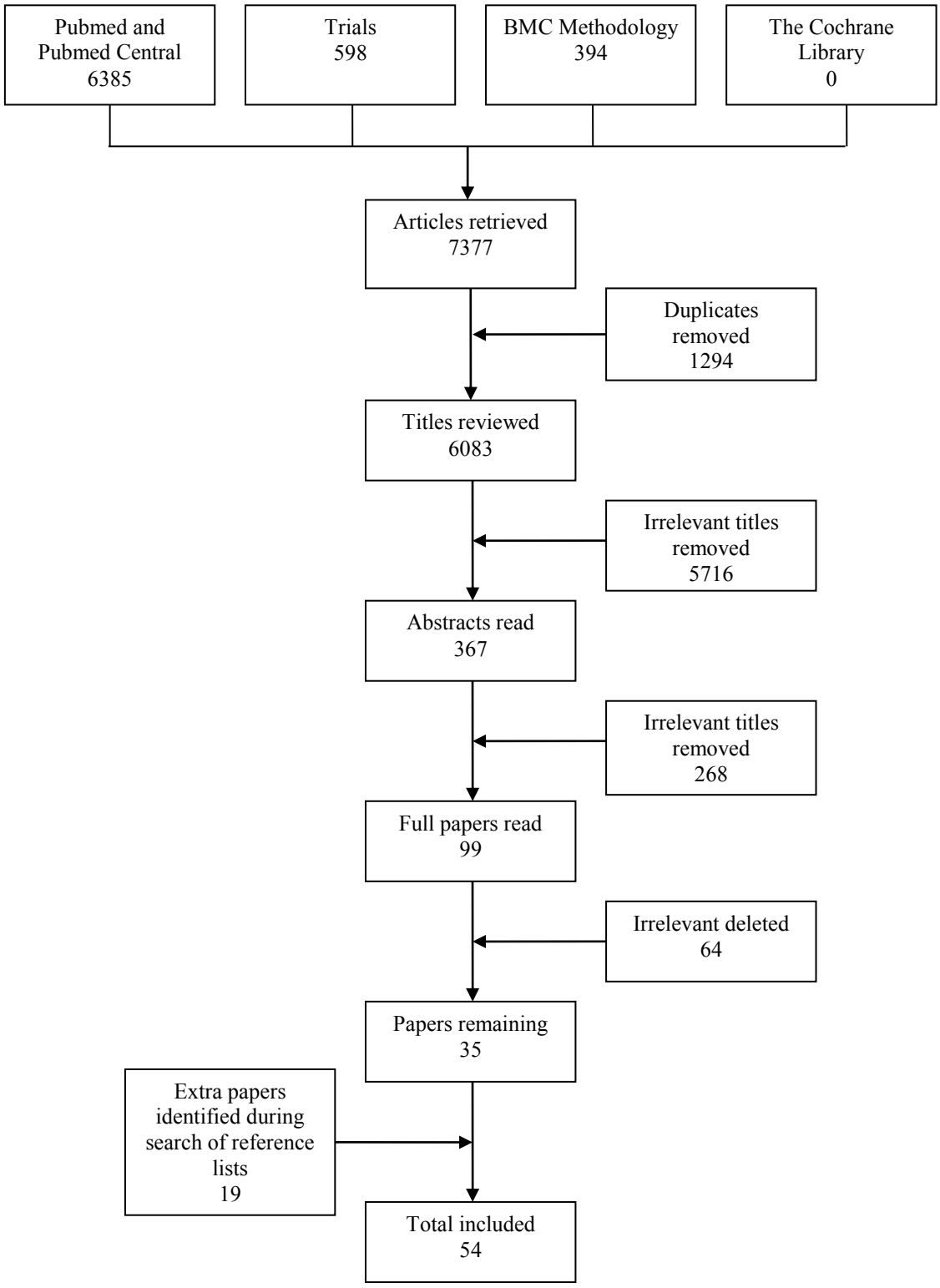
All articles of any study type were eligible as long as they discussed recruitment to primary care based RCTs.

All search results were imported into Reference Manager (version 11) and duplicates were removed. The titles of all remaining articles were screened, and any irrelevant titles were also deleted. Of the remaining titles, where there was any uncertainty about the relevance, the abstract was reviewed for eligibility and irrelevant papers were again excluded. For all remaining potentially relevant studies, full text articles were obtained and assessed for inclusion.

3.2 Results

From 6083 unique titles, 99 articles were retrieved and 35 eligible publications identified. A further 19 papers were identified from the search of reference lists of relevant studies, giving a total of 54 applicable articles. (See Figure 2, page 40)

Figure 2: Primary Care Literature Review



3.3 Discussion of the Evidence Pertaining to Primary Care Based Trials

Factors influencing recruitment to primary care based trials are broadly similar to those affecting trials in all settings (see Tables 3 (page 18) and 4 (page 21).

3.3.1 Physician Willingness to Participate

When looking at trials in general, the recruitment of adequate numbers of physicians or sites was identified as a particular problem for trialists: a number of factors influencing their willingness to involve themselves with trials were identified. (See Table 2, page 13) This issue is also problematic for primary care based trials. In fact, it is possible that it is an even more acute issue in primary care,[65] as these trials typically involve a larger number of sites than trials carried out in a hospital setting. There are a number of articles that have highlighted this issue. (See Table 6, page 42)

Table 6: Summary of Publications included in the Systematic Review

Study	Design	Relevance	Methods and Results
Allsup *et al.* 2002[66]	Retrospective analysis of recruitment to an RCT of influenza vaccination; questionnaire survey of 1173 patients who refused to participate	Identification of eligible patients; impact of information given to patients on their willingness to participate	*Patient Identification:* Only 7/20 (35%) of practices had the necessary skills to identify patients using computers, manual identification of patients in remaining practices was difficult and time consuming. *Questionnaire response rate*: 1173/2583 (45.4%). *Impact of information given on patient willingness to participate*: 25.2% of responders objected to the use of the word geriatric, causing sufficient offence to be sole reason for non-participation.
Asch *et al* 2000[65]	Systematic Review of studies recruiting large numbers of community based physicians where their burden of work is greater than completion of a survey	Physician willingness to participate in research	Sixteen studies identified with GP participant rates ranging from 2.5%-91%. *Barriers:* time pressures; GPs show less interest in research than specialists; incentives (i.e. payment) did not influence recruitment rates. *Facilitators:* affiliation with academic institutions; personal contact by peers; friendship networks.
Askew *et al*. 2002[67]	Postal Survey of 467 GPs and qualitative semi-structured interviews with 18 GPs	GP attitudes towards research	389/463 (84%) of GPs had a positive attitude to research; only 29% of these wanted more involvement. *Barriers:* general practice environment and culture. *Enablers:* academic mentors; reputable established research relevant to general practice; access to information resources, i.e. MEDLINE.
Bell-Syer *et al.* 2008[25]	Postal survey of 124 GPs participating in 2 RCTs of management of low back pain (one exercise trial and one acupuncture trial)	Identification of factors influencing GP referral of patients	*Response rates:* Exercise trial, 64/87 (73%). Acupuncture trial, 27/37 (73%) *Reasons for non-referral:* patients already had other treatments; time constraints; concern for patients (not all patients would get the intervention; patients travelling to classes/clinics); remembering inclusion criteria. *Reasons for referral:* belief in the benefits of exercise/acupuncture; desire to support research; research gave extra treatment option; positive feedback from existing trial patients.

Study	Design	Relevance	Methods and Results
Bower *et al.* 2007[18]	Email questionnaire of 70 corresponding authors who carried out an RCT in UK primary care that were published in the BMJ, Family Practice or BJGP.	Identification of: extent of recruitment difficulties; responses to problems; relationship between trial characteristics and recruitment	*Response rate:* 39/70 (56%). *Extent of difficulties:* Ten trials (29%) recruited to time; 12 (35%) required up to 50% more time than planned; 12 (35%) required over 50% additional time. *Responses to problems:* Extension of recruitment period (56%); seeking additional funds (31%); alternative recruitment methods (18%); recruitment of more sites (44%); recalculating power (21%); completion with insufficient patients (18%). *Relationship:* Only 12.5% trials where GPs were responsible for gaining consent recruited within 50% extra time, compared with 61.5% where GPs were not responsible (P = 0.04).
Bower *et al.* 2009[68]	Narrative literature review	Factors impacting on recruitment; key areas for further research	*Successful recruitment strategies (tested in trials):* Open versus placebo controls; lay advocates/recruiters; alternative patient contact strategies; paper versus electronic data recording. *Further research:* should follow the framework for development of complex interventions; use infrastructure (i.e. Clinical Research Networks) to carry out research on recruitment strategies; evaluation of this infrastructure; development of public and professional engagement with research.
Brealey *et al.* 2007[69]	Comparison of different randomisation procedures in an RCT of early access MRI versus referral to orthopaedic specialist for suspected internal derangement of the knee	Recruitment rate when using postal randomisation procedure instead of telephone randomisation	Randomisation procedure did not affect GP willingness to participate. (155/359 (43%) postal versus 130/288 (45%) telephone) *Patients recruited per practice:* telephone, median 2.5, range 0 -23; postal, median 1.5, range 0-9. 122 (43%) practices recruited no patients. *Factors associated with more patients:* 12% increase with more GPs in practice (p=0.001). *Factors associated with fewer patients:* decrease in 2% with increased practice distance from hospital (p=0.001).

Study	Design	Relevance	Methods and Results
Carr *et al.* 2010[70]	Direct head to head comparison of methods to improve awareness of and recruitment to Alzheimer Disease (AD) trials.	Comparison of Continuing medical education (CME) based event for primary care physicians (PCP arm) versus a grass roots outreach event (COE arm)	*Post PCP course:* PCPs were more likely to: view trial participation for patients as useful (p=0.02); and refer patients to AD trials (p=0.032). They were less likely to see trials as increasing their workload (p=0.0003). There was no influence on the perception of potential risk to patients or fear of losing patients to other healthcare providers. *Post COE course:* no before and after comparison made. 187/250 (75%) attendees agreed to future contact from trials. *Long term outcome:* (4 months post event, defined as enrolment in any clinical research activity): PCP arm = 0 patients; COE arm = 69 patients (p<0.0001).
Davey *et al*. 2003[71]	Comparison of two recruitment methods to an RCT examining cost effectiveness of water therapy for elderly people with lower limb osteoarthritis	Comparison of GP recruitment versus recruitment using the media	*Recruitment methods:* All patients aged 60+ within participating practices were sent a screening questionnaire to determine eligibility. An advert for the trial was printed alongside an article in a local newspaper about the benefits of exercise for osteoarthritis. *Results:* 66 eligible patients recruited during 1 month period via newspaper; 242 recruited via general practice in a 6 month period (40 per month). Recruitment via media yielded fewer patients but was more cost effective (£2.72 per patient versus £27.66 per patient) and more efficient (1 month versus 6 months).
De Witt *et al.* 2001[34]	Survey of 165 GPs recruiting to an RCT of drug treatment for dyspepsia	GP reasons for participation and association of reasons with patient recruitment	128/165 (80%) response rate *Reasons for participation:* research topic (59%); involvement of academic research group (63%); professional obligation (39%); financial incentive (15%) *Factors associated with recruitment rate:* participation of an academic research group (adjusted OR 2.9; 95% CI 1.2-6.9).

Study	Design	Relevance	Methods and Results
Dormandy *et al.* 2008[72]	Qualitative semi-structured interviews with 20 GPs recruiting to an RCT of sickle cell screening.	Physician willingness to participate in research	*Factors important in recruitment:* research topic; invitation method; interest in research.
Ellis *et al* 2007[73]	Retrospective analysis of yield and cost of 10 recruitment strategies used to involve practices in a trial of cardiovascular disease risk factor management.	Physician willingness to participate in research	*Recruitment strategies:* Opt in (i.e. mass advertising; practice meetings; non-personalised mailings; emails from opinion leaders). Opt out (i.e. repeated cold calling; exploitation of professional relationships). Combined opt in opt out (physicians sent an interest survey). *Response rates:* Overall recruitment 68/13823 (0.49%). Opt-in replies 53/13290 (0.40%), recruited 18/53 (34%); opt-in portion of opt-in – opt-out response 90/176 (51%), recruited 19/90 (21%). No results given for opt-out approaches. *Best approaches:* practice meetings (42%); professional relationships (33%).
Foy *et al.* 2002[74]	Survey of trial organisation of seven clinical trials of dyspepsia management, followed by a Delphi technique to reach consensus on quality of evidence to support recruitment interventions	Determination of whether commonly employed recruitment strategies are evidence based	*Methods:* Recruitment methods used in the dyspepsia trials were categorised and deemed to be evidence based if they met criteria I (value established in RCT or systematic review) or II (sufficient face validity that RCT deemed unnecessary) with agreement by 7 out of 9 investigators. *Results:* 56 interventions were identified (median 8 per trial, range 6-9). 35/56 interventions were judged evidence based (interactive educational approaches, educational outreach; dissemination of educational materials). 2/10 organisational characteristics that may influence recruitment were deemed evidence based (eligibility criteria and practitioner workload).

Study	Design	Relevance	Methods and Results
Fransen *et al*. 2007[75]	Case study of recruitment to an RCT of dyspepsia treatment	Description of recruitment strategies	*GP recruitment:* a letter, trial information and recommendation from College of General Practitioners were sent to all GPs. Non-responders were called, and interested practices were visited. 312 GPs participated; 162 (52%) failed to recruit any patients. *Patient recruitment:* by GPs during routine consultation. *Interventions to improve recruitment:* monthly newsletter reminders, minimisation of GP workload; extension of recruitment period (only GPs expected to recruit continued). Recruitment rate did not fall, implying that inclusion of the 'right' GPs may lead to more effective recruitment.
Frayne *et al* 2001[76]	Focus group with a convenience sample of seven primary care providers (PCPs)	Practitioner, attitude and beliefs regarding their role in recruitment to cancer prevention trials	*PCP concerns:* dual role of patient advocate and researcher; threats to primary care relationship (loss of clinical autonomy); general philosophy towards prevention (support for lifestyle interventions, less support for cancer prevention medications); distrust of the research process (research goals may take precedence over optimal patient care); influence of PCP trust for a particular investigator.
Galvin *et al.* 2009[77]	A postal survey of 226 GPs to determine attitudes towards Alzheimer disease (AD) clinical trials	Factors affecting likelihood of a physician to refer patients to trials	*Benefits of referral:* patient benefits from participation; patient interested in participation; participation may enhance care; practitioner may gain helpful feedback to guide care decisions. *Barriers:* perception of risk; patient inability to consent; patient exposure to procedures or extra risk; participation overly burdensome; distance from research site; patient expressed no interest in research; lack of awareness about studies; lack of time during consultations. *Predictors of referral:* close proximity of AD research centre (OR: 4.0, 95% CI: 1.1-15.6). *Barriers to referral:* concerns about procedures or extra risk (OR: 4.7, 95% CI: 1.2-18.7); lack of time (OR: 6.8, 95% CI: 1.4-32.3).

Study	Design	Relevance	Methods and Results
Geraets *et al.* 2006[78]	Evaluation of two recruitment strategies to an RCT of a behavioural treatment for patients with chronic shoulder complaints	Comparison of GP recruitment versus recruitment using the media; comparison of patient outcomes	*Results:* 83 patients recruited by GP, 93 by advertisement. Media recruitment was more efficient (4 month recruitment period by advert versus 14 month recruitment by GP). *Outcomes:* those recruited via GP had greater mean improvements at 52 weeks (p=0.001) irrespective of treatment allocation, indicating that recruitment strategy was a confounding factor.
Graffy *et al* 2010[79]	Telephone interviews with 20 stakeholders (funders, principal investigators, trial managers, ethics committee chairs)	Exploration of practicality and acceptability of undertaking nested trials of recruitment methods	*Barriers:* challenges of implementation (increased complexity and management burden; compatibility between host and nested studies; impact of nested study on trial design and relationships with collaborators; who has control over nested projects and sample sizes). *Enablers:* nested studies should be planned from the outset; good communication between teams; and adequate resources.
Graffy *et al* 2008[80]	Iterative series of 3 workshops, the final one using a modified nominal group technique	Identification of what research staff consider important in successful recruitment	*Research staff opinions:* building and maintenance of relationships (most important factor); primary care teams having positive attitude to research; minimisation of workload and compatibility with practice processes.
Grundmeier R *et al.* 2007[81]	Description of two methods for supporting recruitment using electronic health records (EHR)	Use of electronic health records to improve recruitment	Strategy one: GP recruitment during consultations using computer 'pop-up' prompts as a reminder – clinicians would indicate that the research team had permission to contact the patient. Strategy two: on-site research assistants working from lists of potential subjects derived from the EHR. The use of on-site research assistants to directly enrol subjects generally resulted in enrolment of more subjects.

Study	Design	Relevance	Methods and Results
Hahn *et al.* 2004[82]	Case study of recruitment to a pilot RCT of azithromycin for use in adult asthma	Feasibility of GPs recruiting patients to a practical clinical trial of asthma	3/11 (27%) participating GPs recruited no patients. *Reasons for non-recruitment:* protocol was too difficult; and patients would not consent. *Reasons for sub-optimal recruitment:* eligible patients sometimes overlooked because of busy surgeries (GPs forgot or decided not to discuss the study).
Herber *et al.* 2009[83]	Investigation of the success of different strategies employed to recruit GPs to an RCT of leg ulcer care. Reasons for non-participation collected via telephone.	Physician willingness to participate in research	*Phase 1 recruitment:* Practices contacted by phone with a follow up fax; practices completed questionnaire to determine eligibility (26/1549 (1.7%) participation). *Phase 2 recruitment:* Practice eligibility assessed on the telephone, no need for questionnaire completion (12/273 (4.4%) participation). *Facilitators:* GPs affiliated to universities; use of physician recruiters. *Barriers:* Concern about study workload; disruption to practice routine; general lack of interest in research.
Hummers-Pradier *et al* 2008[84]	Postal survey of 96 German GPs and qualitative interview study of 21 GPs (12 telephone interviews and 9 face to face interviews)	Identification of GPs' motives for non-participation in research and subjective barriers to primary care research	*Survey results:* Research considered important by 88/96 (92%) but 60 (64%) would not take part. 47 (49%) of responders would not allow researchers to have access to their electronic health records, or to allow their patients to be examined by study nurses on their premises. *Qualitative results:* GPs reservations towards participating in research are not merely a matter of time or workload. Concerns include: relevance of the question; not in professional remit of GPs; little value to GP career structure; distrust and negativity towards research and researchers (lack of recognition in the research process, fear of being measured by researchers or concerns about researcher access to data or practice computers), conflict between patient care and participating in research.

Study	Design	Relevance	Methods and Results
Hunt *et al.* 2001[85]	Case study of a failed RCT of structured problem solving and selective serotonin reuptake inhibitor medication for patients with mild depression	Identification of reasons why GPs failed to recruit patients to the trial	*Methods:* The trial followed advice to minimise recruitment problems (recruited GPs with an interest in depression; involved GPs in protocol development; minimised GP workload; exploited CI relationships with participating GPs; amendment of inclusion/exclusion criteria). *GP reasons for non-referral:* lack of equipoise (1 in 6 excluded because of GP treatment preference); restrictive exclusion criteria (protocol amendments did not increase referrals). *Author conclusions:* there needs to be a fundamental shift in ethos and knowledge of principles that underlie research to improve recruitment.
Johnston *et al*. 2010[9]	Mixed qualitative (interview) and quantitative (survey) methods to gather data about practice recruitment from five research teams.	Physician willingness to participate in research	GP recruitment rate ranged from 20-49% *Barriers:* Gaining rapport with front office to gain access to the decision makers. *Facilitators:* Recruitment by physicians (but is not explained by differences in recruitment rates); recognition and reward; perceived interest and relevance; effective communication with GPs. *Recommendations:* GP buy-in and effective communication with GPs are felt to be most important aspects of successful GP recruitment.
Jones *et al.* 2009[86]	Systematic review of trials published in four primary care journals	Identification of the proportions of eligible patients recruited into RCTs to determine the external validity of trials	*Results:* The median eligibility fraction (proportion eligible of those screened) was 83% (IQR 40%-100%); the median enrolment fraction (proportion randomised of those eligible) was 74% (IQR 49%-92%). Number needed to screen (NNS) to randomise one patient was 2.43 (range 1-484). *Author's conclusions:* patients deemed eligible after screening are likely to be randomised, though this may be due to inadequate identification or reporting of the eligible population.

Study	Design	Relevance	Methods and Results
Leathem *et al.* 2009[87]	Description of strategy used to recruit GPs to an RCT of an intervention to improve secondary prevention of coronary heart disease; Qualitative interviews with practitioners to explore perceptions of the recruitment process	Physician willingness to participate in research	GP recruitment rate: 48/165 (33.9%) *Recruitment methods:* Initial telephone contact by Research Nurse (RN) to determine practice eligibility and interest. Interested practices were then visited by nurse. *Barriers:* workload/time; staff issues; interest in question or research in general; insufficient number of eligible patients; realistic information about workload may harm recruitment but aids retention. *Facilitators:* Personal contact, avoiding unsolicited letters.
Margitic *et al.* 1999[88]	Case study of recruitment to the Activity Counselling (ACT) Trial	Relative success of different GP recruitment methods	*Methods:* GPs at only 1 site were directly involved in recruitment but this was discontinued due to lack of recruitment. Patients were otherwise recruited by study personnel. *Results:* Direct mailing was the most successful, yielding 43.4% of randomised patients; questionnaires handed out in practice yielded 32.5%; direct telephone contact yielded 21.6%. *Conclusions:* multiple strategies should be utilised, monitored carefully and adapted as necessary.
Mason *et al* 2007[89]	Qualitative semi structured interviews with 41 GPs participating in an RCT recruiting patients with depression	Practitioner factors affecting patient recruitment	*Themes identified:* concerns about the impact on the doctor/patient relationship and protecting vulnerable patients; perceived lack of skill and confidence introducing the subject of research; the priority given to clinical and administrative tasks over research. *Conclusions:* patients are not always given the chance to participate in research in the same way they are encouraged to participate in treatment decision making. A radical change in clinician attitudes and policy may be needed to give research a higher priority in primary care. Lack of skills should be addressed with increased training for GPs.

Study	Design	Relevance	Methods and Results
McKinstry *et al* 2007[90]	Case study of an RCT of management of Bell's Palsy	Physician willingness to participate in research	*Recruitment methods:* Invitation letters highlighted benefits of participation (benefits to patients; reduction of GP workload due to participation; remuneration). The letters were signed by local 'champions'. *Maintaining interest:* Regular feedback and newsletters.
Monaghan *et al.* 2007[91]	Single blind RCT of the effects on recruitment of communication, involving 167 clinical sites in 19 countries.	Impact on recruitment of increased communication strategy between the central trial co-ordinators and the clinical sites	*Methods: S*ites were randomised to either additional (85 sites) or usual (82 sites) communication strategies. The additional group received a communication package comprising additional, individually tailored feedback about recruitment in addition to the usual correspondence. *Results:* there was no significant difference in the median number of participants recruited between the additional and usual groups (37.5 vs. 37.0, p=0.68). The median time to reaching half the randomisation target was lower in the additional group than the usual group but this did not achieve statistical significance (4.4 months vs. 5.8 months, p=0.08).
Mosis *et al*. 2006[92]	Use of software to allow automated patient identification and recruitment in an RCT of tolerability of celecoxib and diclofenac in patients with osteoarthritis; qualitative interviews with recruiting GPs	Use of computers to identify patients, identification of barriers to using this approach	*Methods:* The software was incorporated into the practice clinical computer systems. Patients with osteoarthritis were identified and an electronic reminder was added to the patient records. When the patient record was opened a study reminder was displayed, and the GP was guided through the recruitment process. *Results:* 170/7127 (2.4%) patients were eligible, and 20/170 (11.8%) were randomised. Reasons for non-inclusion after prompt: seen by a non-study GP (20%); GPs too busy to recruit (20%); GP forgot to recruit the patient (7%). 36% were excluded due to patient related issues. *Qualitative results:* GPs liked the automated process, but specified lack of eligible patients, high number of false positive reminders, and difficulties recruiting patients during routine consultation as barriers to recruitment.

Study	Design	Relevance	Methods and Results
Nelson *et al.* 2006[93]	Qualitative interview study with 13 practitioners (9 GPs and 4 practice nurses) who recruited patients to an RCT of obesity management	Practitioner factors affecting patient recruitment	The intervention was a weight management model; this was implemented with few patients in the trial. *Barriers to recruitment:* substantial misunderstanding about who was responsible for implementation of the intervention; unmet training needs (many forgot about the treatment algorithm or expressed confusion about the mathematical formula they were required to calculate); high expectations about the intervention which became disillusionment as many felt it was merely a refresher of current knowledge. (these practitioners dismissed the study as a 'waste of time').
Paine *et al.* 2008[94]	Analysis of the effectiveness of conducting group seminars with patients prior to screening for a double blind RCT of hormone therapy	Comparison of recruitment rates between patients who did and did not attend seminar groups	*Methods:* Women were invited to attend a group seminar conducted by the research team prior to individual screening for study eligibility. The seminars aimed to increase knowledge about and understanding of the trial. *Results:* women who attended a group seminar were twice as likely to attend screening and enter the trial than those who did not ($p<0.001$). Additionally it was estimated that the time and the number and duration of telephone calls required to recruit were reduced for the seminar group.
Pearl *et al.* 2003[95]	Comparison of characteristics of recruiting and non-recruiting GPs in an RCT to determine usefulness of brain natriuretic peptide in diagnosis of heart failure.	Characteristics of recruiting and non-recruiting clinicians	GP recruitment rate: 186/294 (63%). *Recruitment methods:* Early involvement of GPs in protocol design; detail given about benefits of participation (reimbursement and CPD equivalent points); invitation letters; personal visits to practices. *Results:* Only 49% of participating GPs referred eligible patients (92/186). No differences in sociodemographic characteristics between referring and non-referring GPs were found. The main reason given for non-referral was lack of eligible patients.

Study	Design	Relevance	Methods and Results
Perkins *et al.* 2008[96]	Telephone interviews with staff from practices which expressed interest, took part or withdrew from a trial of a complex intervention for caring for patients with chronic disease.	Physician willingness to participate in research	*Results:* 155 practice expressed interest, and 87 went on to participate. Of those 87, 30 (34%) subsequently withdrew. *Reasons for non-participation*: practice workload; delays between expressing interest and start of involvement (caused loss of interest or involvement in other activities); inability for one person to convince the rest of the staff to participate. *Reasons for subsequent withdrawal:* frustration caused by delays between provision of data and implementation of intervention; realisation of the actual workload; changing practice circumstances (i.e. Loss of key staff). *Practices remaining in the trial:* more likely to see an opportunity to improve chronic disease management and to perceive research as important to improve quality of care in the practice.
Prout *et al* 2003[97]	Qualitative semi-structured interviews with 9 GPs recruiting to a double blind placebo controlled RCT of treatments for upper respiratory tract infections in children	Practitioner experience of participating in an RCT	*Themes identified:* difficulties with recruitment and concerns about safety of study medication; insufficient time to recruit during consultations; ideas for successful trial implementation (including good organisation; simple documentation (especially for patients) and study procedures; ability to allay concerns about patient safety).
Raftery *et al* 2009[98]	Review of guidelines governing payments to clinicians for recruiting to trials. Qualitative semi-structured interviews with a range of NHS clinical trial leaders	Motivators to GPs to participate in research	Participants agreed that research expenses should be covered but that payment in excess of expenses may increase participation but risks reduction of quality. Motivators such as interest in the topic, scope for patient benefit and intellectual curiosity were considered more important. Reduction of bureaucracy and delay are important facilitators.

Study	Design	Relevance	Methods and Results
Raina Elley *et al* 2007[99]	Comparison of two recruitment strategies to an RCT of a multifactorial falls prevention programme	Effectiveness of different recruitment strategies	*Methods:* Patients received study information and a simple study questionnaire asking if they had a fall or trip in the preceding 12 months. In recruitment strategy one, the information and questionnaire were handed to the patient by the receptionist when they entered their practice. In strategy two, the information was mailed to all those in the age group (75+) on the practice register. *Results:* 312 patients were recruited in total. There was a statistically significant difference between the proportion of those screened in the waiting room who participated, and the proportion of those who were screened via post (90/729 (12.3%) versus 222/2705 (8.2%) respectively) ($p<0.001$).
Reid *et al*. 2001[100]	Case study of recruitment to an RCT of the treatment of hypertension in the elderly	Physician willingness to participate in research	Peer to peer recruitment was the most successful strategy. Multifactorial approaches seem to work including: targeting of GPs working in areas with high proportion of relevant population (relevance to their practice demographics); minimisation of workload; face to face meetings and personal contact with GP.
Richardson *et al*. 2002[57]	Cross sectional postal survey of 98 GPs who had agreed to recruit patients for an RCT of breath testing for *H. Pylori* in patients with dyspepsia.	Identification of factors associated with patient recruitment by GPs	Response rate: 95/98 (97%). 53 (56%) of participating GPs recruited no patients. *Factors associated with recruitment:* GPs who had help from practice nurses were more likely to recruit than those who did not. Of the 46 GPs who had nurse help, 26 (56%) recruited, while 16 (33%) without help recruited ($p=0.02$). *Factors not associated with recruitment:* Age, sex, number of GPs in the practice, and number of half days worked.
Ried *et al* 2008[101]	Cross sectional postal survey of five groups of general practice registrars who participated in a 'Registrar Research Workshop' (RRW)	Impact of training on GP skills, confidence, participation and interest in research	Response rate: 77/121 (64%). *Results:* Self-reported research skills increased for the whole group ($p=0.047$), most significantly for those with little prior research experience ($p<0.001$). Two thirds of respondents had been research active, while 84% indicated a high degree of interest in taking part in research in the future. The RRW provides a model for effective training for interested GP trainees.

Study	Design	Relevance	Methods and Results
Rollman *et al.* 2007[102]	Cross sectional comparison of recruitment data from two trials to treat anxiety disorders	Comparison of electronic medical record reminder versus waiting room case finding strategy	*Waiting room recruitment:* study recruiter was stationed in waiting room and administered a questionnaire to determine patient eligibility. *Electronic medical record reminder:* Electronic prompt to remind GP about the trial during routine consultations for anxiety disorders. *Results:* Electronic medical record reminders resulted in 176/794 (22%) patients; waiting room recruitment resulted in 193/8095 (2.4%) patients. *Authors' conclusions:* Electronic reminders may increase efficiency by reducing the burden imposed on practice staff and study personnel.
Rosemann *et al* 2004[103]	Cross sectional study using semi-structured interviews with a random sample of 76 GPs who are involved in the teaching of medical students	GP attitudes to research and reasons for participation/non-participation	85% of GPs appreciated research in their field. *Barriers:* scepticism about research (perceived gap between theoretical research and practical work of GPs; and the domination of research by specialists); clinical workload; Disease Management Programmes and administrative overload. *Biggest motivator:* substantiation of their quality of care with solid research data.
Salmon *et al* 2007[104]	Qualitative interviews with 23 GPs who declined to participate in a research trial to manage medically unexplained symptoms	Interpretation of significance and interrelationship of barriers to GP participation	*Reasons for non-participation:* lack of time; protection of their patients from researchers (concerns about unethical research, confidentiality, coercion, risk to patients); lack of research skills; research has no professional status (seen as irrelevant to GP careers and they feel that they don't have responsibility to do it); they place little value on research because it is uninteresting; concerns about loss of clinical autonomy. *Authors' conclusions:* Lack of time is given as a reason for not participating, but that is justification rather than explanation. The underlying concerns are what really deter GPs from participation. It is possible that payment will release more time, as GPs are more likely to use their own time if payments are made.

Study	Design	Relevance	Methods and Results
Sanders *et al*. 2009[105]	Case study of recruitment to an RCT of vitamin D3 versus placebo for older women at risk of hip fracture	Comparison of recruitment strategies	*Recruitment strategies:* Doctor referral; presentations at clubs; church/club newsletter; word of mouth; media; targeted mail outs. *Results:* 1716/2317 (74%) of patients were recruited in the last 5 months following a targeted mail out. Prior to this, only 541 women were recruited over an 18 month period. Targeted mail out recruited 1629 (70%) of patients; GPs recruited 116 (5%) of patients.
Sherber *et al* 2009[106]	Questionnaire study of patients to determine whether their willingness to participate in a trial is influenced by whether their personal physician rather than an unfamiliar physician was study investigator	Influence of relationship between the patient and the physician	*Response rate:* 789/1132 (70%) with 666 having complete data. *Results:* Patients were likely/very likely to participate 56% of the time if asked by their personal physician compared to 36% of the time if asked by an unfamiliar physician ($p<0.0001$). *Authors' conclusions:* this finding could relate to the importance of communication, trust and familiarity with the health care system.
Sibthorpe *et al* 2002[107]	Interviews with health care professionals recruiting to a failed RCT of the effectiveness of a brief intervention for hazardous alcohol use.	Reasons why patients were not recruited	*Results:* Project processes did not fit with clinic processes and was seen as a 'hassle'; alternative processes favoured by clinic staff did not fit study protocol; health workers uncomfortable approaching people about their drinking and uncomfortable about implementing the intervention; health workers considered randomisation unethical on one hand, and 'like telling people what to do' on the other hand.
Stuardi *et al* 2010[108]	Discussion of advantages and disadvantages of identifying potential participants using database recruitment	Identification of participants	*Advantages:* Identification of large numbers of potential patients quickly and easily (computer search); quick delivery of study materials via bulk mail out; can be scheduled to take place at a time convenient to the practice; elimination of subjectivity that may accompany GP referral. *Disadvantages:* Restricted to identifying patients with chronic conditions; may include patients who do not meet inclusion criteria; may include people inappropriate to contact (i.e. recently deceased).

Study	Design	Relevance	Methods and Results
Van der Windt *et al* 2000[109]	Illustration of problems related to patient recruitment to an RCT comparing corticosteroid injections and physiotherapy for painful stiff shoulder	Reasons for non-referral and efforts to overcome poor recruitment	*Reasons for non-referral:* busy surgeries; forgetfulness; conviction that a patient would benefit more from a specific intervention; lack of eligible patients; restrictive trial procedures. *Interventions to improve recruitment:* monthly newsletters; reminders; six monthly practice visits; prompt and adequate feedback to queries about trial procedures. *Authors' conclusions:* As not all participating GPs recruit it may be more useful to identify GPs motivations to participate and target those interested and experienced in research rather than recruit as many GPs as possible.
Wadland *et al* 1990[62]	Comparison of recruitment to an RCT of smoking cessation in two primary care sites, and a randomised trial of how consent was gained in one of the sites	Comparison of different ways of recruiting and gaining consent	*Site one:* private family practice with 5 physicians (ages 35-62) and 15,000 patients. All patients were given a screening questionnaire on entry to the practices and smokers were informed about the trial. *Site two:* academic general internal medicine practice with 6 physicians (aged 32-58) and 16,000 patients. Interested smokers were randomly assigned to having the form explaining the study read to them by the study co-ordinator (actively informed group) or the patient reading the information alone (self-informed group). *Results:* The rate of enrolment was 3.3 times greater in the private practice than the academic practice (45% versus 14%). There were no difference in recruitment rate between the actively and the self-informed groups (27/51 (53%) actively informed versus 25/52 (47%) self-informed)

Study	Design	Relevance	Methods and Results
Ward *et al* 1994[29]	Follow up study (using self-administered questionnaires) of 134 GPs participating in the Men's Health Study to elicit their feedback about the study	GP perceptions about participating in research	*Factors influencing decision to participate:* research topic; telephone call from PI prior to written information; co-ordinator visit; GP interest in research. Decisions to participate influenced more by topic and personal visits than by names and track record of research team. *Positive aspects of study:* prompt to remind GPs to talk about urological problems; quick and easy protocol; increasing patient awareness about urological problems; patients liked practice to take part in research. *Negative aspects of the study:* negative reactions of some patients; age restriction of the protocol; demands on time; extra workload; inappropriate timing of the study.
Wilson I *et al* 2000[37]	Postal questionnaire of 636 GPs who participate in clinical trials	Differences between recruiters and non-recruiters	*Response rate:* 636/1518 (41.9%). Of these 169 (26.6%) had not recruited any patients to any study. *Differences between recruiters and non-recruiters:* wish to learn more about research (74.8% versus 63.8%); desire a good relationship with staff (63.9% versus 53.1%); involvement worthwhile (83.1% versus 54%); too embarrassed to ask (39.5% versus 22.7%); patient refusal (81.2% versus 63.2%). All findings are statistically significant (all $p<0.02$).
Yeomans Kinney *et al* 1998[110]	Survey of 175 women at increased risk of breast cancer who discussed the possibility of their inclusion in a trial with their GP	Impact of GP recommendation for involvement in a trial	Women who reported that their GP advised them to participate in a trial were 13 times more likely to participate than women who reported that their GP advised them not to participate (OR 13.09, 95% CI 2.64-64.77).

3.3.1.1 Interest in the Study Question

One factor cited as an issue that impacts on the willingness of clinicians to participate in trials is interest in the study question, and this remains true for GPs. Seven papers reported that interest in the question encouraged them to take part, or cited lack of interest as a reason for declining participation.[9,29,72,83,84,87,90] One of the main aspects of a trial that will encourage GP interest in a question is its perceived relevance to their everyday practice: relevance encourages personal interest in the topic[83] and is a 'cornerstone for the GPs decision' to participate.[84] GPs will consider the population mix of their practice and will consider the relevance to their patients when considering participation. In an interview study, one GP stated that one of the reasons they took part was because 'we have a very high proportion of people from the relative… ethnic minorities, so it seemed sensible for us to do it'.[72] Although this finding is true to all trials, there seems to be an extra hurdle to overcome when recruiting GPs rather than specialists and this may be reflected in the fact that there are lower participation rates amongst GPs than other specialities.[65] GPs seem to have less interest in research in general, with some questioning the relevance of research at all:[67,83] these practitioners were unlikely to become involved with trials.[67] Eight papers[67,72,80,83,84,87,103,104] cited a general lack of interest in research as a problem that needs to be overcome in order to improve GP participation, and they put forward a number of reasons to explain why they place little importance on it. (See Table 7, page 60)

Table 7: Reasons given for GP Lack of Interest in Research

Value of Research from GPs Perspectives
Relevance to a primary care career ➢ A different career structure to that of specialists means that there is no need for GPs to carry out research or to publish papers[104] ➢ Research is outside the professional remit of a GP[84] ➢ In a hierarchy of activities for GPs, research was low in its clinical or professional value[84,104] Relevance to general practice ➢ Preference for using clinical experience over research evidence for clinical decision making[67,104] ➢ Clinical practice is unscientific, so it is not possible to base everything on evidence[104] ➢ Evidence based medicine is incompatible with person-centred care[83] ➢ Researchers are interested in the wrong things. The question does not always relate to problems in general practice[104] and can be perceived as being only of academic interest and to benefit the researcher's career[103] ➢ General practice is inherently not researchable[104] Personal feelings ➢ Ambivalence or negative attitude to research[84] ➢ Sense of entitlement not to be involved in research[104]

Despite a number of articles having identified lack of research interest as a reason for non-involvement, it remains unclear what impact this has. The 3 papers that seemed to cite the most negative attitudes towards research in general come from Germany,[83,84,103] so it is possible that there is something specific to the German health system that promotes this outlook. In their case study discussing reasons for GP non-participation in a trial to treat leg ulceration, Herber et al describe a health care system where GPs feel that they have a lower status in the community care sector than specialists, and do not perceive that research activity helps to enhance their professional standing.[83] Two qualitative interview studies carried out in the UK demonstrate that this attitude towards research is not unique to Germany: they found that some British GPs also place little value on research.[89,104] Some were sceptical about its value[89] while others contrasted research with the 'real work of clinical practice', feeling that it was not professionally relevant and they 'don't have the responsibility to do it'.[104]

It is possible that this negative outlook exists in other health systems, although the extent of this problem must be kept in perspective. Rosemann et al interviewed 76 GPs who were involved in the teaching of medical students: while the negative views some German GPs have towards research is discussed, this study also found that 85% of GPs appreciate research in their field.[103] They also conclude that a positive attitude towards research was the most important motivation for a GP to participate; only those who were research active said that participation 'improves the reputation of GPs and documents our quality of care'.[103] However, as they only interviewed GPs who carry out undergraduate teaching at the University of Heidelberg, it is not clear whether these findings would relate to other GPs. Given that a number of studies found that GP affiliation with a university was an important facilitator for participation,[34,65,83] it is possible that the interviewed GPs may have atypical attitudes towards research.

In contrast to the findings of Rosemann et al, two survey studies found that many GPs have a positive attitude towards, or an interest in research. A postal survey of 96 German GPs found that 92% of them have an interest in research,[84] while a survey of 463 Australian GPs found that 84% of them had a positive attitude towards research.[67] Unfortunately their interest did not translate into willingness to participate (only 36% of interested German GPs and 29% of interested Australian GPs would become personally involved) so the impact of lack of interest on involvement remains unclear.

This is a difficult area for trialists to introduce interventions that may improve site recruitment rates. Graffy et al carried out a number of workshops that consisted of a group of experienced trialists. The aims were: to identify factors that they consider important in successful recruitment; and their confidence in achieving them. 72% of workshop attendees considered that primary care team positive attitude was important, and most were fairly confident about how to address this. However, in order to raise the profile of research and to ensure that it is a normal part of everyday activity, they felt that there need to be changes to the organisational culture of the health service: trialists were less sure about how to achieve this.[80] It would appear that research needs to be made an integral and rewarded part of primary care culture and to achieve this, changes would need to be introduced at a national level: individual research teams are therefore unlikely to have a significant impact on this problem.

3.3.1.2 Ability to Carry out the Study

Even when a GP is interested in research and believes the question is important enough to consider taking part, there are a number of practical considerations that are also taken into account when deciding whether or not to participate. As was found when looking at trials in all settings, these centre around their ability to carry out the work involved. Time constraints are often felt to be a major barrier to involvement: Five articles were found that cited this as a

reason for non-participation.[65,87,100,103,104] In one case 100% of interviewed GPs cited it as a reason for not taking part[104] while 50% of GPs invited to take part in a trial of coronary heart disease prevention also stated they did not have enough time to carry out the study.[87] A number of surveyed GPs stated that they were already overworked by their daily routine, and the administrative workload place on practices on a daily basis contributed to this.[103] Given the relatively low importance placed on primary care based research, it is therefore unsurprising that many GPs are unwilling to take on this extra workload.

In an attempt to address this problem, trialists often aim to encourage participation through minimisation of practice workload by streamlining data collection techniques,[65] or keeping protocols simple.[83,87,90,103] To further minimise workload, two trials required GPs only to identify patients and then refer them to the study team who will determine eligibility and gain informed consent.[87,90] Both of these trials met or exceeded their expected recruitment targets, but it is not clear whether this minimisation of GP workload actually encouraged their involvement. Having interviewed 23 GPs who declined participation in a trial to manage medically unexplained symptoms, Salmon et al concluded that GPs cite lack of time as a reason for non-participation, but this actually masks other concerns.[104] For example, while it would seem logical to reduce workload by providing research nurses who parachute into practices to carry out the bulk of study work, this may introduce other concerns: a number of GPs expressed fears about being measured by researchers, or about giving research nurses access to their patients or computer systems and cited this as a reason for not being involved in research.[84,104] It is entirely possible therefore, that removal of one barrier is simply replaced with another.

3.3.1.3 Other Factors

When looking at trials in all settings a number of other factors were cited as being influences on participation to research, and these too, seem to remain relevant when looking at primary care specifically. Again, the evidence is not clear cut.

Personal relationships

Exploitation of professional relationships through the use of a local 'champion' to encourage participation is cited as a motivator to participation.[90] No studies have tested the impact of this approach so it is not clear whether or not this actually works. Use of peer to peer recruitment is also thought to increase GPs willingness to participate and is cited in a number of papers: GPs are thought to be more likely to participate if they receive an invitation to take part by one of their peers.[9,65,83,100] Once again the success of this is unclear. Reid et al, when recruiting practices to the Second Australian Blood Pressure Study (ANBP2) found it to be their most successful strategy.[100] Herber et al used research nurses to telephone clinicians to invite them to participate, but found it difficult to get past the barrier of reception staff. They concluded that use of physicians to contact GPs would allow them easier access to the doctors who would make the decision about participation. Unfortunately they were unable to test this theory due to financial constraints.[83] Another study used mixed qualitative and quantitative methods to examine physician recruitment to five trials.[9] They found that, although the projects using physician to physician recruitment believed that this was a key factor in successful recruitment, this did not explain differences in participation rates. For example, the Cardiovascular Health Awareness (CHAP) study employed local physician opinion leaders as one approach to practitioner recruitment. They recruited 49% of approximately 700 invited GPs. In contrast, the Improved Delivery of Cardiovascular Care (IDOCS) study, which used similar recruitment methods, recruited only 19% of 1077 eligible GPs.[9] Johnston et al

conclude that the mixed flexible approach employed by CHAP was a more important factor than use of peers for successful GP recruitment.[9]

Participation of academic research groups

Impact of the involvement of an academic research group on site recruitment in primary care based trials is unclear. Trust in the researchers carrying out the trial may influence participation. For example, affiliation with a respected research institution is said to be associated with successful GP participation.[83] However, in another study, some GPs expressed suspicion that a covert aim of the institution was to divert patients away from them and to the University in question,[65] and as a consequence were reluctant to participate. GPs cite a general mistrust of researchers and their motivations as a barrier to participation;[84] the research can be seen as unethical, with GPs citing concerns around coercion and confidentiality.[104] Development of good working relationships may help overcome some of these problems.[80]

3.3.2 Interventions to Improve GP Participation

The use of incentives has been used in an attempt to improve GP participation in research. Although financial gain is not cited as an important reason for taking part, GPs do report that the lack of remuneration is a barrier to participation.[95,104] It seems that, while GPs do not wish to make a profit from research, they do need to be reimbursed for the time spent working on the study.[95,98] Payment may encourage them to use otherwise free time for taking part in research or may be used to buy locum time to cover the loss of the GP from usual practice.[104] Other incentives include access to specialists that would not form part of routine care;[90] the attainment of Continuous Professional Development (CPD) points;[96] invitations to presentations of the findings;[96] or access to information resources not otherwise available.[67]

However, whilst incentives are often employed, none of these studies examined the effectiveness of these measures.

A number of articles have reported different approaches to site recruitment.[83,87] These are mainly focussed on the initial approach to practices. Many studies utilise a Dillman or Modified Dillman approach to recruitment.[111,112] This typically involves an initial mailout, followed by a second mailout and then a telephone call. Herber et al tried two slightly different approaches. In the first, practices were initially contacted by telephone, and those expressing an interest in the study were sent a fax and were asked to complete and return a questionnaire; the response rate for this questionnaire was very low (only 105/741 (14%) of those expressing an interest during the telephone call returned a completed questionnaire). This approach resulted in a 1.7% practice participation rate in the trial. Their second method was to remove the requirement for questionnaire completion; all other aspects remained the same. This resulted in a 5.1% practice participation rate in the trial. It is not clear why the need to complete a questionnaire seems to have had some impact on physician recruitment rates. It may be that this requirement deters some because it gives them the impression that the study will involve large amounts of paperwork completion.[83] Another survey of recruiting GPs found that initial telephone contact from a clinician associated with the study encouraged some GPs to take part, with 48/134 (36%) of them stating that 'this encouraged me a lot'.[29] While these findings suggest that telephone contact may be a useful approach when recruiting practices, the experience of Herber et al implies that the benefits of initial telephone contact can be easily undone by the requirements of the study.[83]

A trial to improve cardiovascular disease (CVD) risk management employed 10 different approaches to clinician recruitment which included opt-in and opt-out strategies, and a

combination of both.[73] A number of approaches used a professionally designed colour flyer. The poster was either posted alone or with a covering letter, or was faxed to practices with a covering fax; the fax produced the best absolute response accounting for 13 (19%) of their recruited sample (fax recruitment rate 13/3882, <1%). There were other small differences between the approaches (for example, the covering letter sent with the fax was signed by the Principal Investigator (PI), while the letter accompanying the postal invitation was sent on the headed paper of the local NorthWest Area Health Education (AHEC) network of primary care practices, and was signed by their director) so it is not possible to determine whether it was the fax approach alone that accounted for its apparent success.[73] Furthermore, the fax invitation was one of the more expensive methods of recruiting sites, so may not be the most cost-effective approach. However, it is difficult to interpret these findings as the authors state that individual sites may have received multiple opportunities to participate via a variety of approaches.

3.3.3 Clinician Factors that Influence Patient Recruitment

As discussed in section 2.3.3.1, not all participating clinicians go on to actually recruit patients successfully. This also seems to be pertinent to primary care based trials[69,95] and this next section will focus on practitioner factors that may influence recruitment. It is acknowledged that concerns about any of the following factors may also deter a GP from participation, but the literature focuses on how they influence the recruitment of participants once a practitioner has agreed to involvement. Therefore, these factors will be discussed in relation to how they impact further down the recruitment flow, primarily on the identification, selection and enrolment of eligible patients. (See Figure 1, page 10)

3.3.3.1 Impact of Clinician Motivation to Participate on Patient Recruitment

Only one article was found that looked at whether motivation to participate impacted on patient recruitment rates once a decision to become involved had been taken.[34] The authors surveyed 128 GPs (response rate 128/165, 80%) who participated in an RCT of drug treatment for dyspepsia. They asked questions about personal and practice characteristics, and about reasons for taking part. Eight motivators (topic; academic research group; sponsor; clinical research organisation; financial incentive; trial presentation; personal appeal; professional obligation) were compared with patient recruitment and they found that only 'motivation (for involvement) by the academic research group' was independently associated with the number of patients recruited (adjusted OR 2.9, 95%CI, 1.2-6.9).[34] It remains unclear whether a GP's initial attitude to the study is reflected in their success or otherwise of recruitment: identification of those clinicians most likely to recruit well would allow trialists to focus their resources more effectively.

3.3.3.2 Equipoise

As detailed in section 2.3.3.2, a clinician needs to be in equipoise for each individual patient for it to be ethical for them to enrol that patient into a trial. When looking at recruitment to trials in general, this was identified as a barrier to recruitment in a number of studies. In the literature pertaining to primary care based trials, equipoise was discussed explicitly only once.[85] This was in an RCT of structured problem solving and selective serotonin reuptake inhibitor (SSRI) medication for patients with depression. The authors conclude that, given the obvious differences between the trial arms, GPs decided which approach would suit individual patients early in the recruitment process, and this had a negative impact on accrual (20% of the potentially eligible patients were not considered suitable for one of the treatment arms by their GP).[85] However, as this conclusion is based on speculation by the authors, it is not clear that this was actually the reason that GPs were reluctant to recruit to this trial.

Equipoise was mentioned indirectly in two further papers. Van der Windt et al, in a case study of an RCT for treatment of painful stiff shoulder, report that GPs cite the 'conviction that a patient would benefit more from a specific intervention' as a reason for non-referral. Unfortunately they do not quantify the problem, or investigate it further.[109] Bell-Syer et al compared recruitment in two trials treating back pain. The intervention being tested in one study was acupuncture, in the other exercise classes. In both trials, uncertainty about the benefits of the intervention reduced the willingness of some GPs to refer their patients. However, this was only cited as a reason by 9% of the respondents across both studies. 33% of GPs actually preferred the intervention and were deterred from referring patients because they were not guaranteed that treatment (patients had a 50% chance of being offered exercise or 66% chance of receiving acupuncture). Conversely, 34% of GPs involved in the same studies and who had a belief in the potential benefits of the intervention were more willing to refer their patients for trial entry because it gave them potential access to treatments that may otherwise not be available.[25] It is difficult to interpret these findings with respect to the impact of equipoise on recruitment: while 33% of GPs were deterred from referral because of a preference for exercise or acupuncture, 34% of GPs were encouraged to recruit to the same trial for the same reasons. It may be that differences in services available locally account for this finding, but it is not possible to elucidate further from the information given in the paper.

3.3.3.3 Factors Influencing the Informed Consent Discussion

Clinician concerns regarding the process of informed consent impact upon the recruitment process to RCTs in general, but they seem to be less of an issue for primary care based trials. One qualitative study interviewed 41 GPs who were recruiting to an RCT treating depression.[89] This study found that GPs differ in their ability to introduce the concept depending upon their confidence in their knowledge of the trial. GPs describe the process as

their ‘sales pitch’ and develop stock phrases that they are comfortable with. Their ease with this was also dependent upon how research active their practices are: those in less active practices sometimes felt uncomfortable introducing research as their patients would not be expecting it. Some described research as being intrusive and disrupting to the normal flow of the consultation, and were concerned that if they did not introduce it confidently it may compromise the patient’s trust and confidence in them.[89] This qualitative study indicates that some GPs may have concerns about discussing trials with their patients, while others are less worried. There is no discussion about how this translates into actual recruitment, whether GPs who express more concern are less likely to recruit their patients. Furthermore, this article examines recruitment to a trial of depression; consultations with depressed patients may differ from other consultations and could impact on a GPs willingness to discuss the trials in a way that is not evident in trials in other disease areas.

3.3.3.4 Impact on the Doctor/Patient Relationship

When looking at trials in general, concerns about the impact of recruitment to trials on the Doctor/ Patient relationship were often cited: this was also identified as a concern in primary care based trials. This section will examine how far the concerns already identified relate to a primary care setting.

Discussion of Uncertainty

As discussed in section 2.3.3.2.2, one of the drivers of the Doctor/Patient relationship is the physician expert knowledge. The need to discuss uncertainty about the best treatment was uncomfortable for clinicians and led to them selecting patients with whom to discuss the research. This was identified as a problem in two primary care based trials.[85],[89] In their article examining recruitment to a failed trial, Hunt et al did not identify worries about the discussion of uncertainty as a problem influencing recruitment, rather they felt that their GPs lacked the

confidence to deliver the intervention effectively.[85] In contrast, a study that interviewed GPs recruiting patients to a trial treating depression did find that the acknowledgement of uncertainty was a barrier to recruitment.[89] GPs felt that patients with depression preferred their GP to make treatment decisions for them, and were concerned that uncertainty would jeopardise the patient's trust in them.[89] However, within the same study, other GPs held contrasting views. They felt that the introduction of the topic of research in a consultation could actually strengthen the relationship as it indicates a greater interest in the patient's welfare.[89]

Dual role of GP and Researcher

The difficulties faced by clinicians who are acting in the dual role of doctor and researcher, and the concern about the negative impact this may have on the doctor/patient relationship has been identified as a factor that impacts negatively on recruitment to trials in general. Three primary care based studies discussed this issue but in little detail. In one interview study, some GPs perceived a degree of divergence between their clinical goals and those of researchers, and as such, were sometimes reluctant to introduce the subject with their patients.[89] Hunt et al had similar findings, concluding that the change from practitioner to researcher was too great to facilitate a shift in behaviour, and that this inherent contradiction is a basic problem for clinical research.[85] However, this article was descriptive and is based only on author speculation, and so it is not possible to determine whether this contradiction actually did contribute to the trial's failure. The issue was explored in more detail by Frayne et al. They conducted a focus group study with 7 GPs with the aim of assessing their attitudes towards recruitment of their patients to cancer prevention trials.[76] They found that some GPs expressed considerable concern about this perceived conflict in roles. They felt that trying to act as the patient's advocate within the health care system whilst also enrolling them in a trial

would ‘erode their relationship with the patient’. GPs used terms like ‘crossing the line’ or patients say’ Wait a minute. Who are you working for?..... Me? Or is it just that you want to sign me up for a research study’.[76] However, they also found that where GPs have faith in the trialists or the PI, they were willing to ‘spend’ some of the trust that they had banked with their patients and recruit to the trial despite their concerns.[76] As patients were found to be more likely to consent to participation if their personal physician, rather than an unfamiliar physician, is the investigator[106,110] and patients are becoming more accustomed to shared decision making,[89] it is possible that this paternalistic, protective attitude, whilst well meaning, is actually misplaced. Patients may like to be given the option of taking part in research, and would like the opportunity to make the decision for themselves.[89]

There are relatively few articles discussing concerns about the impact on the doctor/patient relationship in primary care based trials and the evidence from these is conflicting. It may be that GPs have a different relationship with their patients than specialists do, and so the introduction of the subject of trials into the consultation holds fewer concerns for GPs. It is also possible that GPs who do hold these concerns choose not to participate at all, so the impact of worries about the effect on the relationship is minimal. However, given the small amount of research in this area and it is not possible to draw firm conclusions on the true impact of these concerns on GP recruitment of patients.

3.3.3.5 Clinical Autonomy

The concern about the loss of clinical autonomy when involving patients in trials was explored in two studies. In a focus group study, GPs described difficulties in the co-ordination of care within primary care, and described it as a ‘loss of control over clinical management’; they were concerned that, in the extreme, this might lead patients to abandon continuous care entirely.[76] There is an argument that autonomy in medicine has been challenged in recent

years and that growing reliance on evidence based medicine further dis-empowers individual practitioners.[113] In light of this, after interviewing 23 GPs, Salmon et al conclude that GPs feel the need to preserve their sense of individual professional autonomy by emphasising the individuality of their clinical work. GPs emphasised the importance of clinical experience over evidence, which in turn caused them to maintain their distance from anything associated with evidence based medicine. The authors conclude that loss of autonomy is a substantive barrier to GP involvement.[104]

3.3.3.6 Structural Barriers

A number of other barriers to recruitment were identified that are also relevant to primary care. These have the potential to impact on any point in the recruitment flow.

Time constraints

As previously discussed, time constraints play a role in whether or not a GP will take part in a trial. However, once they have made the decision to participate, the necessary time commitment may still make it difficult for them to actually recruit patients. Busy surgery hours were commonly cited by GPs as a reason for failing to recruit or refer patients.[107,109] This is especially true for trials that need to recruit patients during routine consultations:[92,97] the need to gain informed consent is seen as a '*time-consuming disruption of the normal work flow*'[92(p 501)] Other GPs say that the need to pick out patients in the middle of surgery puts them under pressure.[97] Some trials use a practice nurses to share the workload. They help in a variety of areas, including: administration; obtaining informed consent; identification of patients or reminding GPs about the study. One study found that GPs who had the assistance of a nurse were significantly more likely to recruit than those who did not (56% of GPs with nurse help recruited versus 33% of those who did not, $p = 0.02$).[57] Foy et al carried out an examination of existing literature to determine whether any of the recruitment strategies

commonly employed were evidence based. They concluded that use of a researcher to carry out recruitment is one of the few evidence based strategies that improves recruitment.[74] These findings do imply that reduction of workload will increase the ability of practices to recruit. It is possible that the involvement of different types of staff could be equally beneficial, as could the use of researchers to carry out recruitment. However, as already discussed, this could merely remove one barrier only to replace it with another.

Staff shortages

Lack of staff, specifically support staff, was identified as a barrier to recruitment to trials in general, and may impact on the ability of GPs to recruit. When looking at the literature pertaining to primary care based trials this is not discussed directly in any papers, so it is not possible to ascertain how relevant this remains.

Research experience and training

Lack of experience or training was also shown to be an issue influencing recruitment to trials in general. However, in relation to primary care based trials, only one article discussed the relation between experience and recruitment. This survey found no association between prior research experience and the number of patients recruited, although confidence intervals are wide, so an association cannot necessarily be ruled out (OR 1.5; 95% CI 0.6-3.6).[34]

Identification of eligible patients

Another issue that seems to affect recruitment to primary care based trials is the identification of sufficient numbers of eligible patients. Despite efforts to estimate the number of potentially eligible patients, trials often suffer from a phenomenon referred to as Lasagna's Law.[37,109,114,115] Lasagna's Law is attributed to Dr Louis Lasagna, who noted, in the 1970s,

that as soon as a study starts the theoretical pool of 100% of patients instantly drops to 20%, and goes back up to 100% at study conclusion.[115,116] This could be attributable to a number of reasons: overestimation of disease prevalence; decrease in the prevalence of the disease in question;[57] inability to identify all potentially eligible patients; the restrictiveness or otherwise of inclusion/exclusion criteria; or the time available to recruiters.[109] If trialists have based their recruitment projections on disease prevalence alone, it is possible that they have set themselves an impossible recruitment target, as identification of potentially eligible patients has been reported to be problematic within primary care. Practices often lack the computer skills to run the necessary reports.[117] When patients need to be recruited during normal consultations, GPs report that they often forget about the study, resulting in potential patients being missed.[109] Furthermore, calculations often do not allow for exclusion of patients who are considered unsuitable by their GP.[109]

3.3.4 Interventions to Improve Recruitment to Primary Care RCTs

3.3.4.1 Identification of Eligible Patients

A number of interventions have been tried with the aim of overcoming the problems posed by Lasagna's Law. One approach is to improve the use of computers.[81,92,102,108] One article discussed the development of a computerised reminder system that could be integrated with practice systems. It would remind GPs about the study when the record of a potentially eligible patient was opened, and would guide the GP through the recruitment procedure. Despite the reminder popping up on the computer screen, the approach was not entirely successful: 6.5% of GPs still forgot to enrol the patient, and others still found the requirement to obtain informed consent during routine consultations too time consuming.[92] These findings are supported by those of Rollman et al. They compared a computerised prompt for recruitment based on specific criteria from electronic medical records (EMR) with a waiting

room based recruitment process, which involved a researcher being stationed in the surgery waiting room. The researcher would screen patients for eligibility through use of a questionnaire, and where appropriate, would carry out informed consent. This study found that fewer than 5% of referrals were made via the EMR.[102] These findings should be interpreted with caution in the context of improving GP enrolment, as the EMR was not compared directly to the referral rates of GPs without the use of EMR. It is possible that the findings actually reflect that recruitment in the waiting room is simply a more successful approach.[88,99]

Stuardi et al examine the recruitment rates of a number of studies that utilised the EMR system to perform database searches to identify potentially eligible patients in an attempt to maximise the number of potentially eligible patients who are identified. They compared the recruitment to four studies using this approach with that of two studies that asked GPs to approach patients during regular consultations. They found that all trials using EMR recruited on time and above target, whilst the studies using the GP approach either extended their recruitment period or failed to reach their required numbers.[108] As already discussed, recruitment during regular consultations is problematic, so these findings may merely reflect those difficulties. However, there may be potential for use of computer systems to influence recruitment rates in a number of ways: further research would identify the most successful ways of doing this.

Trialists often send recruiting GPs newsletters and reminders about the study, or carry out regular site visits in an attempt to keep the trial at the forefront of their minds.[109] Clear, timely communication between sites and study teams is also thought to improve recruitment. However, an RCT looking at the effects of enhanced communication between central trial co-

ordinators and clinical sites failed to show a significant difference in accrual rates between the additional contact and usual contact groups.[91] Advice to trialists is to ensure that inclusion/exclusion criteria are as unrestrictive as possible, to maximise the numbers of potentially eligible patients, thus avoiding the need for protocol amendments that may require lengthy changes to trial approvals.[17] Protocol amendments to relax these criteria are sometimes made, and study procedures are often streamlined or simplified in an attempt to improve a poor recruitment rate.[2] These approaches are often based on logical assumptions rather than evidence: no trials testing these approaches have been identified.

3.3.4.2 Different Approaches to Recruitment

A number of articles were identified that had tried to improve recruitment to primary care based trials by using different techniques. Paine et al invited all patients who may be eligible for their trial to an education seminar prior to recruitment by their GP. They found that women who attended the seminar were twice as likely to consent to participation than those who did not, and that GP time spent screening their patients and discussing the trial with the seminar group was reduced.[94] However, as patients self-screen, there is the potential to introduce selection bias, so the researchers advocate the use of an RCT to determine the role of seminars on patient recruitment.[94] Another approach was to test the use of postal randomisation as opposed to the usual telephone randomisation technique.[69] This involved patients completing and posting baseline material to the study centre, where randomisation took place when received. The intervention was not successful: it actually reduced the number of patients recruited, although this finding was not statistically significant.[69] Two studies compared GP recruitment with use of the media to advertise the study.[71,78] Both studies found the media to be a useful tool in improving recruitment: it was faster and more cost effective.[71]

This approach should be used with caution, as one of these studies did find differences in disease characteristics and preferences at baseline between media and GP recruited patients.[78]

3.3.5 Comparison of Recruitment to Primary and Secondary Care Based RCTs

The evidence pertaining to recruitment issues in primary care based trials is broadly similar to that relating to trials in other settings. Similar problems are cited, and no factors were identified that were unique to primary care based trials. However, the primary care based literature differs in its emphasis. In contrast to general trial settings, much of the primary care literature relates to the problems encountered when recruiting sites or investigators, and how to overcome them: in general trials, the focus is on factors that influence the process once the physician has agreed to participate. Recruitment of secondary care sites to trials seems to be less problematic than recruitment of primary care sites. This may reflect the different career structure for physicians in these settings: hospital doctors aiming to be consultants may find their career prospects enhanced by publication; GPs have no need to do so, and therefore may be less interested in research involvement.[104]

When considering the recruitment of patients once a physician has agreed to participate, similar issues were raised, for example, concern about the doctor/patient relationship; issues encountered during the informed consent process; or practical barriers. However, in primary care based trials there seems to be fewer studies examining these issues than there are when looking at secondary care based trials. This could be for a number of reasons: maybe the focus of research in primary care has been on the recruitment of practitioners rather than patients, and these problems are actually more acute than is reflected in the literature. It is possible that these issues are genuinely less of a concern in primary care than they are in secondary care: GPs may be in a position to develop different relationships with their patients than those

experienced between specialists and their patients, as they can develop these relationships over a long period of time.[118] Differences in the relationship may mean patients have different expectations from their GP than they do a specialist, and so makes it easier for a GP to introduce the possibility of research participation. This may account for the different focus in the literature. It may also be that GPs are much more selective about participation than hospital clinicians. With less pressure to publish because of differing career structures,[104] GPs who are concerned about any of the issues may simply decide not to take part at all; specialists, in contrast, may become involved and find that their concerns about discussing trials only come to the fore when faced with individual patients.

3.3.6 Current Guidance on Recruiting to RCTs

The Primary Care Research Network (PCRN) Recruitment Methods Group have published a Practical Guide to Primary Care Research Recruitment which is a resource for researchers involved with the practicalities of patient recruitment.[17] It was developed through the use of focus groups with stake holders and aimed to bring together the experience and knowledge from a variety of research active professionals. The authors hope that it will inspire others to adopt procedures that they may otherwise not have thought about, thus achieving their targets. The document is comprehensive and offers practical tips on a range of issues, from governance and approvals to 'selling' the study to potential participants.

The guide gives advice on developing a feasible recruitment plan, and advises those who wish to recruit patients through primary care to carefully consider whether alternative approaches, for example, direct targeting of specific patient groups, would be more appropriate. They give suggestions for addressing Lasagna's Law, including: methods of identifying suitable patients; consideration of the content of the patient information sheet; examination of how the study is explained to participants; suggestions to overcome the barrier of investigators who

are too busy to enrol patients. There is a chapter devoted to the recruitment of primary care collaborators, giving advice on areas such as identification of collaborators, being explicit with practices about both direct and indirect benefits of participation, use of incentives and careful consideration of the anticipated roles of primary care staff.

This practical guide is a very useful document. It addresses many of the common pitfalls encountered in primary care research, gives good advice on how to overcome the problems and tallies with the problems identified in the literature search. It is an effective way of tapping into the wealth of experience of researchers. However, it does not negate the need for further research into the subject: the combination of experience (around which this practical guide was largely based) and a sound evidence base may lead to improved recruitment to trials.

3.3.7 Conclusions

Factors that influence recruitment to trials in general are also applicable to trials carried out within the primary care setting, although in this setting the emphasis in the literature is placed more on the recruitment of sites than the recruitment of patients: in hospital based studies, the opposite is true. As with all research, it needs to be carried out in the appropriate setting: the underlying issues of recruitment in primary care differ enough from those encountered in hospital settings to render much of the current literature of limited applicability. While there were reasonable numbers of articles identified in the literature search, it is evident that there are still no solutions to the problem of recruitment. Although observational data or case studies of individual trials are useful starting points, even when taken as a whole there is no clear picture of exactly what the causes of the problems are, or what the effective solutions may be. The evidence is often contradictory or inconsistent, and may not necessarily paint the

full picture, as with the possibility that the barriers to recruitment attributed to time constraints are actually covering up the fact that there are more complex reasons why GPs choose not to participate.

There is a complicated interplay of issues that influence recruitment to trials. In primary care, further research needs to be carried out in virtually all areas of recruitment in order to fully understand the problems and to identify and test potential solutions. Given the number of components that could contribute to the problem, studies should be carefully considered, and carried out with consideration of the MRC guidance on developing and evaluating complex interventions.[119]

One approach is to consider a study that was initially failing to meet recruitment targets but which was ultimately successful: no papers were identified that have done this.[2] It would be useful to examine the recruitment strategies undertaken in such a trial and to ascertain whether there were identifiable time points where there were significant changes to recruitment rates. Although studies of this type cannot provide evidence of cause and effect, any findings could provide a useful springboard for the design of future intervention trials. The Birmingham Atrial Fibrillation Treatment of the Aged Study provided such an opportunity.

3.3.8 Limitations of the Literature Review

The main limitation of this literature review is that bias may have been introduced, which can make it difficult to judge its quality and reliability. Bias may have been introduced in a number of ways. Firstly, only one person (myself) identified the papers and extracted the data. Good quality systematic reviews use more than one reviewer to identify and code the studies, and report the level of agreement between the individual reviewers. This ensures consistency

and reliability of identification and coding. Use of only one reviewer may therefore result in inappropriate inclusion or exclusion of studies, or in non-systematic data extraction. Secondly, bias may have been introduced through the lack of formal quality assessment of included studies. Quality assessment uses previously agreed indicators to determine whether individual studies were of sufficient standard to provide reliable results. The lack of formal assessment in this review may therefore have led to the inclusion of evidence provided by poorly designed studies that may themselves provide unreliable evidence. Thirdly, a date limit was used to exclude a number of studies: articles prior to 1990 were not included. Systematic reviews aim to identify all evidence pertaining to the research question; date limits may result in the exclusion of important articles. Although it is acceptable to implement time frames where appropriate, it must be acknowledged that this may result in the loss of important evidence. Finally, ascertainment bias may have been introduced into this review due to the exclusion of studies that were not published in the English language, if those published in other languages were systematically different to those published in English. For example, English language journals tend to have a higher impact factor than foreign language journals, so it is possible that included studies show more 'positive' results than excluded ones. In this subject area, positive results may mean that publication is more likely for trials that do not reach their recruitment targets as lessons can be learned from these failed trials (See section 2.2). Therefore, ascertainment bias as a result of the exclusion of non-English language papers may have resulted in important missed information.

Despite the limitations discussed in the previous paragraph, the impact of bias on this review is felt to be small. Although it is acknowledged that bias may have been introduced through the use of one reviewer and the lack of formal a priori criteria to assess quality, the simplicity of the inclusion criteria ensured that any bias would be kept to a minimum. All studies,

regardless of their design, were included if they discussed practitioner or practice factors influencing recruitment to an RCT: the subjectivity of a single reviewer was therefore minimised. Informal quality assessment was carried out (i.e. the strengths and weaknesses of individual studies were discussed but no formal checklist to enable systematic quality assessment was followed) and the limitations of individual studies were included in the discussion. This ensured that the aim of including any issues that were identified was achieved. The date limit and exclusion of non-English language papers may mean that factors that influence recruitment were missed. However, it was decided to exclude articles prior to 1990 because they often discussed the need for written informed consent. This consideration is not relevant to current trials because written consent is a requirement; the debate surrounding this issue is therefore no longer applicable and it was felt that exclusion of older papers would not, therefore, result in a significant omission. It is plausible that exclusion of foreign language papers may have omitted important factors. Unfortunately, resource limitations rendered translation impossible, and any bias that may have been introduced by this remains.

3.4 The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) Study

This section will provide the background to the BAFTA study. It will summarise the original protocol and give details about the practical aspects of the trial, for example, how patients were identified and which staff carried out individual roles. As the thesis is focussing on the recruitment of patients, study follow up procedures and data analysis will not be discussed in any detail. However, this has been reported elsewhere.[120] During the recruitment period, changes were made both to the protocol and the processes. These amendments will be relevant to the rest of the thesis, and will be detailed in the appropriate chapters.

3.4.1 Study Design

The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study was a primary care based pragmatic RCT of aspirin (75mg/day) versus adjusted dose warfarin (Target INR 2.5, range 2-3) for stroke prevention in older people (aged > 74) with atrial fibrillation (AF).[120,121]

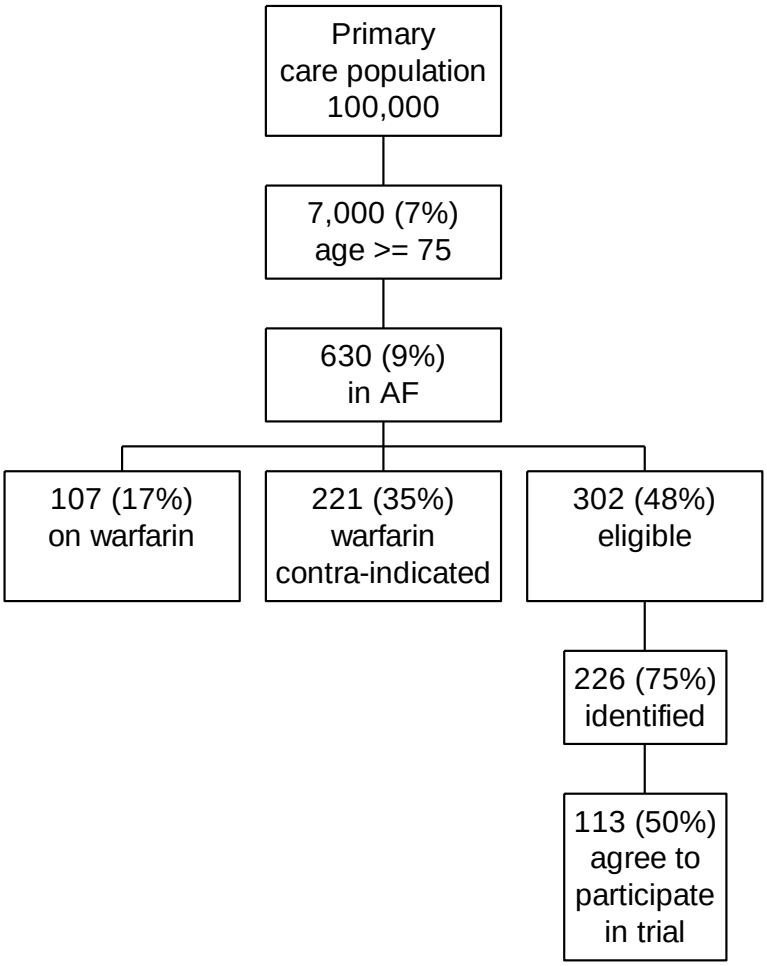
3.4.2 Sample Size and Recruitment Estimates

The study aimed to randomise 1240 patients (620 in each arm) and follow them up for an average of three years. Based on published data regarding the prevalence of AF in this population, it was estimated that a total practice population of 1,097,000 would be required, comprising 76,800 aged > 74. This equated to 157 practices with an average list size of 7,000, and recruitment of 8 patients per practice. (See Figure 3) Patient recruitment was expected to start in January 2001 and last for two years.

3.4.3 Practice Recruitment

Practices were located in the West Midlands, although it was anticipated that the trial would extend to other regions (Gloucester; Oxfordshire; Cheshire; Warwickshire; Worcestershire). It was intended to recruit larger practices in preference to smaller ones. All GPs within the practice were sent a letter inviting them to take part in the study, together with information about the study and the expected workload. Interested GPs returned a faxed reply slip, and were sent an invitation to attend a study training session. The agenda for the training session can be found in Appendix One. After the training, practices made the final decision about whether or not they would take part.

Figure 3: Expected Recruitment Rates



3.4.4 Study Aims

The aim of the study was to provide evidence of the risks and benefits of warfarin and aspirin therapy in an elderly population in atrial fibrillation drawn from primary care. The primary aim was to:

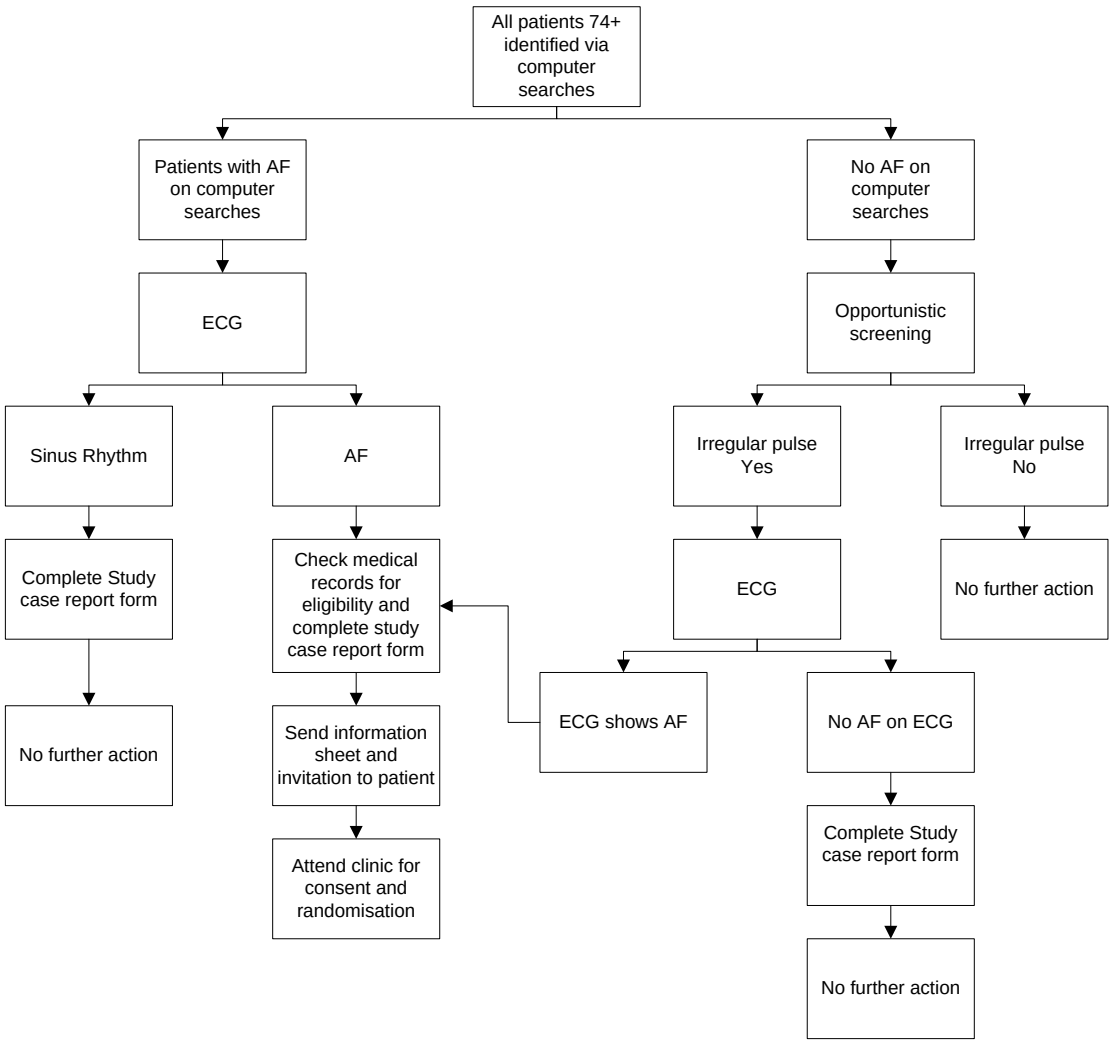
- Compare the incidence of fatal or non-fatal disabling stroke or significant systemic embolism in patients treated with adjusted dose warfarin or aspirin.

3.4.5 Study Design

The study was a randomised controlled trial of warfarin versus aspirin for prevention of stroke in elderly patients identified in general practice with atrial fibrillation confirmed by

electrocardiogram (ECG). In all participating practices, a computer search to identify all patients aged > 74 was carried out. Within this population, patients were identified in two ways: further computer searches and by opportunistic screening of the pulse by practice staff. The recruitment strategy is summarised in Figure 4.

Figure 4: BAFTA Study Recruitment Strategy



3.4.6 Computer Searches

These were tailored towards the information that was held on the computer in each practice. If practices held AF registers, or used READ diagnosis coding, then these were used.

Additionally, searches on prescriptions of digoxin, anti-arrhythmic agents, aspirin or warfarin were carried out. The case notes of patients identified in any of these searches were reviewed for a diagnosis of AF. If present, patients were invited to attend the practice for an ECG. Patients identified in this way were classed as the Case Note Review (CNR) group.

3.4.7 Opportunistic Screening of Pulse

A flag was placed in the case notes of all patients aged ≥ 75 who were not invited to an ECG clinic as a result of the computer searching described above. In paperless practices, electronic prompts were used instead of paper flags. These prompts were to remind any member of the primary health care team to check the pulse the next time they saw the patient. The result (regular or irregular) was recorded, and if irregular, then the patient was invited to attend the practice for an ECG. Patients identified in this manner were classed as the Opportunistic Screening (OS) group.

3.4.8 Confirmation of AF by ECG

Patients identified in either of the ways described above were invited to attend a dedicated nurse-run clinic at which a 12 lead ECG was performed. The ECG was sent to the central study office for verification of diagnosis by a cardiologist. ECG results were then returned to the practice.

3.4.9 Patient Eligibility

Once an ECG diagnosis was returned to the practice, patients were reviewed for eligibility: the Practice Nurse reviewed the patients' medical records for evidence of absolute exclusion criteria. (See Table 8)

3.4.10 Patient Information and Consent

Case Note Review patients were sent an information sheet and an invitation to attend an ECG clinic. Opportunistically Screened patients were given the information sheet during the ECG

clinic unless they met any of the absolute exclusion criteria. Patients with ECG confirmed AF were then invited back to a randomisation clinic appointment. During this appointment, the ECG results were discussed, and eligibility for the trial assessed. The GP obtained written consent from those patients who would like to take part. (See Table 9, page 89)

Table 8: Initial Study Inclusion and Exclusion Criteria

Inclusion Criteria
➢ Age ≥ 75 ➢ Atrial fibrillation or flutter confirmed by ECG
Absolute Exclusion Criteria
➢ Known rheumatic heart disease ➢ On warfarin ➢ History of major non-traumatic haemorrhage (e.g. gastro-intestinal) ➢ History of intra-cranial haemorrhage ➢ Endoscopically proven peptic ulcer disease in preceding year ➢ Known allergic hypersensitivity to either of the study medications
The Uncertainty Principle
➢ If a GP was certain that a patient should not be entered into the trial, for whatever reason, then that patient was not eligible ➢ If a GP was uncertain whether or not warfarin was indicated, then the patient was eligible ➢ This decision was made on a case by case basis after consideration of all relevant factors, including: o Factors increasing the risk of haemorrhage set against high risk of stroke in these patients

3.4.11 Practice Staff Roles and Anticipated Workload

Each practice nominated a GP and a practice nurse (PN) who would be responsible for identifying and recruiting patients within their practice. They would attend an initial full day study training session which would encompass study paperwork and procedures, and GCP training in relation to the study. The roles and responsibilities of each practice member were explained, together with a discussion about the anticipated workload and details of reimbursement to the practice. It was anticipated that practices would complete their patient recruitment over a 12 month period, and follow up would continue for an average of three years. Full details about the roles and workload can be found in Table 9 (Page 89).

The BAFTA study was initially failing to reach its recruitment targets. (See Figure 5, page 88) The research team implemented a number of changes: protocol amendments; practical changes that influenced both the work flow and workload for practice staff; increased the number of participating practices; and extended the recruitment period. A new power calculation was carried out and a revised target of 930 patients was set (the original target was 1240 patients). It was calculated that this target would enable the study question to be answered in the context of meta-analysis with the existing literature. The revised target was eventually exceeded (973 patients recruited). As such, BAFTA provides the ideal opportunity to investigate the recruitment process and the remainder of this thesis will focus on analyses of recruitment to this trial.

Figure 5: BAFTA Recruitment Targets

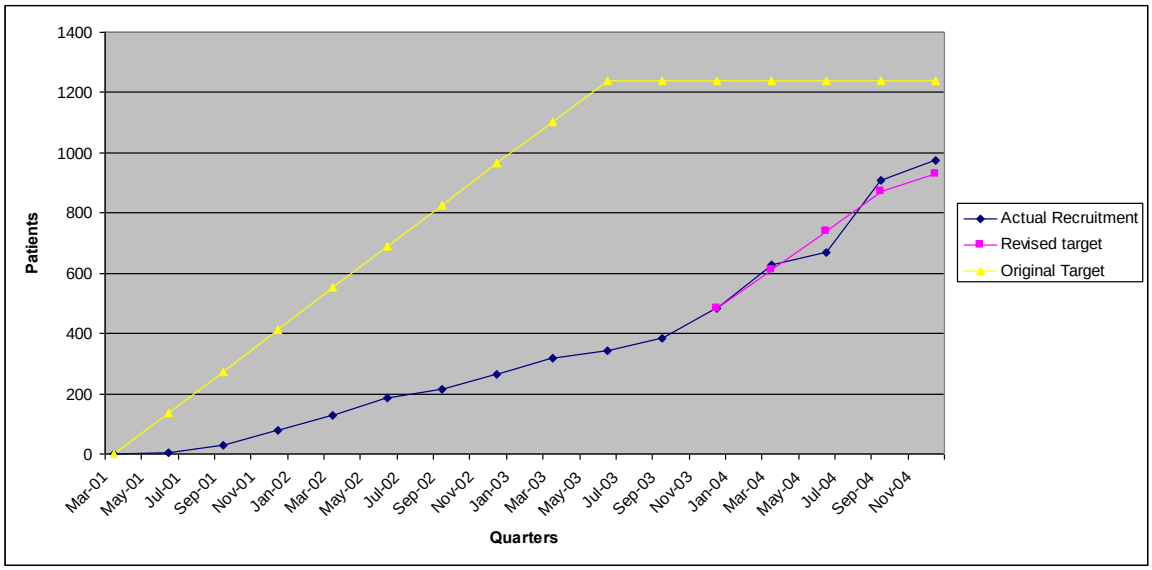


Table 9: Staff Roles and Workload

Task	Staff Type	Info Collected	Estimated time	Total numbers expected per practice (7000 ave)	Total estimated practice time**
Computer search	RA	AF status on patients aged 75+. Drug information	N/A	490 aged 75+ 245 AF + 245 AF -	N/A
Patient notes tagged for OS	Reception	N/A	One off task	470 notes	8 hours
ECG Clinic	Practice Nurse	Patient reported medical history; current medications; carry out ECG; initial discussion about trial	Average 20 mins per patient	119 patients	40 hours
Case note search for medical history	Practice Nurse	Case note reported medical history; current medications; AF evidence	Average 10 minutes per patient	36 patients	6 hours
Decision about patient eligibility	GP	Using case report form (CRF) completed by PN during case note search of medical history	Average 5 minutes per patient	36 patients	3 hours
Randomisation Clinic Appointment	PN/GP	PN Patient questionnaires (Rankin; EQ5D; SF12); memory test; baseline blood pressure; GP Double check eligibility; discuss trial and obtain informed consent; call randomisation telephone line	PN Average 20 minutes per patient GP Average 20 minutes per patient	31 patients	PN 10.5 hours GP 10.5 hours
Patient Follow up*	GP	Adverse events; endpoint and hospital admission information; change in medications; Rankin	20-30 minutes per patient	8 patients	23 hours (over 3 year period)

* follow up information enclosed to give an idea of the expected practice workload
** total estimated practice time involvement 101 hours.

Chapter 4: Choice of Methodology

As discussed in section 3.3.5, although there is a growing body of literature examining the issue of patient recruitment to trials, analysis of data from a trial that demonstrated identifiable change points in recruitment would be useful:[2] the BAFTA Study provided the opportunity to do so. It was decided that a mixed methods approach would be the most appropriate way of addressing this study question, as recruitment to trials seems to be a complex area, and there is a dearth of good evidence available: mixed methodology can accommodate both of these issues. This chapter will outline the reasons for choosing this approach and will introduce each stage separately: Stage One, factors that predict patient consent to take part in an RCT (Chapter five); Stage Two, trends in the recruitment of patients to BAFTA (Chapter six); Stage Three, understanding the experience and attitudes of GPs who recruited patients to BAFTA (Chapters seven – nine).

4.1 The Mixed Methods Approach

Although mixed methods research has been controversial[122] and is still developing, it is becoming increasingly common in health services research. [123] It is characterised by the use of both qualitative and quantitative approaches to data collection and analysis[123,124,125] and aims to integrate the findings from both techniques in order to 'offer insights that could not otherwise be gleaned'.[126] It is a useful approach to use when the question is complex, or if there is little existing evidence in the area. Greene et al developed a conceptual framework for mixed methods research identifying five different purposes, any one of which would make it appropriate to adopt a mixed methods approach.[124] Two apply to this study: development; and expansion. The first, development, 'seeks to use the results from one method to help develop or inform the other method, where development is broadly construed to include sampling and implementation'.[124] In this project, the results from the first two stages informed the design of

the third phase. Full explanation of individual methodologies are given in the relevant chapters, but essentially stage one and two results informed both the sampling and the topic guide used in the final phase.

The other mixed methodology purpose appropriate to this study is elaboration. This was defined by Brannen as where 'qualitative data analysis may exemplify how patterns based on quantitative data analysis apply ….the use of one type of data analysis adds to the understanding being gained by another'.[123] In this thesis, the aim of the final stage of this project was in part to identify potential explanations for the existence of patterns found in parts one and two, therefore elaborating on the findings of the first phases.

As is the case with other mixed methods studies, the questions addressed by this study cannot be comprehensively answered by one method alone. The use of both qualitative and quantitative methods allows for a more detailed understanding of this complex question, with each approach being suited to a different aspect of the project. The mix of techniques offers a more comprehensive way of investigating a GP's view of enrolling patients into an RCT and how this may influence their ability to recruit successfully, than a single methodological approach would allow.

Despite the strengths offered by a mixed methods strategy, there are potential pitfalls in using this approach. There are fundamental differences between both the approach and the theoretical underpinnings of quantitative and qualitative paradigms, and there is controversy surrounding their combination.[122,125] Furthermore, additional skills are needed to combine such different methods, which pose additional challenges for the researcher. However, in order to fully address the questions of the study, it was felt that the benefits of using this

approach outweighed the disadvantages, and would provide more useful information for other researchers looking to address the issue of poor recruitment to their trials.

4.2 Individual Methods

This section will look at the individual study questions that this thesis aims to address and introduce the methods used to answer each question. This introduction gives a brief overview of the individual research question and the methods used: full details of the methods employed will be given in the relevant chapter.

4.2.1 Stage One: Factors that Predict Patient Consent to take part in an RCT

Stage one aims to determine whether there are any patient and/or practitioner factors that predict whether or not a patient will give their consent to participate in an RCT. As discussed in section 2.3.3.1, simple involvement of clinicians as local investigators for multi-centred studies does not necessarily lead to good patient recruitment, and the discrepancies between the number of practitioners who agree to participate and the number of those who actually recruit is often cited in the literature.[35] The reasons for this are not clear. Extensive literature exists that cites problems with the consent process as being a major barrier to recruitment,16 but these often focus on patient understanding and acceptance of the issues under discussion:[2,4,127] there is little research looking at whether there are practitioner or patient factors that influence the process. Better understanding of what makes some practitioners recruit well may enable trialists to identify practitioners who would be most likely to recruit successfully, thus enabling research teams to optimise resource use. Analysis of patients invited to take part in BAFTA would address this question. Therefore, a cross sectional study using logistic regression analysis was carried out to determine which patient and/or practitioner factors predicted consent.

4.2.2 Stage 2: Trends in the Recruitment of Patients to BAFTA

Stage two aims to identify whether protocol or procedural changes in BAFTA were associated with changes in patient recruitment. As described in previous chapters, there is a growing body of literature surrounding the issues of recruitment of patients to trials, and the methods used to overcome these barriers. Although there are few trials testing recruitment interventions, the available evidence does indicate that how the trial is conducted can influence accrual rates. In contrast to this assumption, there is an argument that it is not possible to make design changes that will improve recruitment to a trial that does not initially recruit well.[128] (See Section 6.1) This stage will examine the impact of study design on patient recruitment and will address the question: was the increase in recruitment over time due to an increase in the size of the study population as a result of expansion of the number of active sites, or was it due to changes in study design and conduct? An observational time series analysis of patient recruitment to BAFTA was conducted to achieve this aim.

4.2.3 Stage 3: Understanding Experience and Attitudes

As discussed in Chapter 3, although the attitude of GPs towards research has been examined in a limited fashion, there has been little work done that looks at the experience of GPs recruiting their patients to trials. Analysis of recruitment data from BAFTA (discussed in chapters five and six) will allow identification of factors that may influence patient recruitment, but will not provide any understanding as to why any influences exist. Therefore, the aim of this stage of this project is to understand the GPs experience of participating in this study, from their decision to participate through to study close down and, where possible, to identify any patterns within the data that may provide theories as to the reasons for any influences. It is anticipated that development of these theories will provide a springboard for subsequent work that may help trialists overcome some of the barriers to recruitment.

There are no easy quantitative ways to measure an individual's experience, as it comprises many personal and subjective issues. Qualitative methods are better suited to exploring this area as it is the most appropriate way to explore why individuals act in a particular manner; to explore new areas; or to address sensitive issues.[129] Qualitative study can gain rich descriptions and explanations of processes in local contexts; Miles and Huberman describe how it can preserve chronological flow, thus indicating which events lead to which consequences.[130] For example, they are referring to how rather than just finding out that a GP did not enrol as many patients as anticipated, they may say they did not enrol because they could not identify eligible patients, or they were not comfortable with the trial interventions. Here, qualitative investigation allows the researcher to gain more insight into causation by having the opportunity of probing the reasons for the effect.

Initially it was decided that this study would use a grounded theory approach to data collection and analysis.[131] It was considered an appropriate methodology as there is little existing knowledge in this area and grounded theory is a useful tool in 'the investigations of relatively unchartered waters'[132,133] It is also allows the development of theories that can then be tested in subsequent projects. There are a number of central aspects to grounded theory, including theoretical sampling and constant comparison analysis: these are described in more detail in Chapter 7. However, as described in section 7.7, a modified approach to grounded theory was eventually utilised, taking into account the researcher's intimate involvement in the BAFTA Study.

Having established that the most appropriate method to use for this phase of the project is a qualitative approach, it was decided that individual semi-structured interviews would be the best data collection method. Focus groups were considered as an alternate data collection

method. There would have been a number of advantages to using this approach: fewer focus groups than interviews would need to be conducted, especially useful where there are time limitations; discussion of some subjects may be stimulated by the group environment; and it may be possible to include the views of more people by carrying out a few focus groups than it would by choosing to use individual interviews. However, there are also a number of disadvantages: the logistics of organising groups can be problematic, especially when the population in question are geographically diverse or a particularly busy group of people; discussion of potentially sensitive topics can be difficult in a group setting as people may be less willing to talk about their experience or opinions; and the composition of the group needs to be carefully considered. For example, if a focus group consisted of employees and employers, the employees may find it more difficult to be involved in the discussions. For subject areas or populations where it would be difficult or inappropriate to carry out focus groups, individual interviews are often the most appropriate method to use; they minimise the potential logistic issues, making it easier to reach otherwise difficult to access populations, and they provide the respondent with an environment in which they have the confidence to discuss difficult or sensitive topics.[134]

For three main reasons it was decided that individual, semi-structured interviews were the most appropriate data collection method for this stage of the study. Firstly, the population in question (GPs) are difficult to access for research[135,136] because they are a particularly busy group of people. It was felt that they were more likely to participate if their involvement could be carried out at a time and location suitable for them; the logistics of organising focus groups would be difficult. Secondly, they were a very geographically diverse population, with GPs potentially being as far apart as Sheffield, London and Cornwall. Again, the logistics were considered to be impossible for a focus group approach. Thirdly, it was felt that the subject

under discussion could be potentially sensitive; GPs were likely to be discussing how they communicate with their patients, how they feel about involving their patients in trials, and how well, or otherwise, they recruited to the study. It was felt that interviews would potentially allow GPs to discuss these topics more freely.

Having discussed the methods that were employed in this project, the thesis will now go on to discuss each stage in detail.

Chapter 5: Factors that Predict Patient Consent to take part in a Randomised Controlled Trial

5.1 Background

As discussed in Chapter 4, better understanding of the factors that influence consent is needed to enable trialists to plan their studies appropriately. The literature search (Chapter 2) identified three articles that examined the impact of clinician motivation for participation on patient recruitment rates.[33,34,37] These have been described in detail in section 2.3.3.1, but essentially they looked for associations between the reasons given by physicians for participating and patient recruitment rates. Two of these studies were carried out in a primary care setting.[34,37] They were postal surveys of recruiting GPs and included questions about GPs' reasons for agreeing to take part in a trial. The authors found a positive association with recruitment rates for those ranking the involvement of an academic group highly (adjusted OR 2.9, 95% CI 1.2-6.9)[34] and for those expressing an interest in research per se (74.8% recruiters wanted to learn more about research versus 63.8% of non-recruiters $p<0.023$),[37] and a negative association for those who ranked personal appeal by the research team as an important motivator (OR 0.4, 95% CI 0.2-0.9).[34] All other factors showed no association with recruitment rates. These findings indicate that practitioner factors impact on whether or not a patient will give consent. However, they are restricted to why a clinician agreed to take part and do not take any other factors, for example, practice demographics or GP experience, into account.

BAFTA provided an ideal opportunity to conduct analysis that may identify factors that influence consent, as it was a multi-centred trial carried out throughout England and Wales and involved large numbers of GPs. Although the recruitment target was achieved, patient

entry was slower than anticipated and required a re-structuring of the recruitment strategy to achieve study power within a reasonable timescale. Over the four year recruitment period, the number of participating practices was increased, and it was initially assumed that this expansion of the available patient pool was responsible for the study's ultimate success. As it is possible that patient, practice and/or practitioner characteristics influenced recruitment to the study, a cross sectional study of patients invited to take part in the BAFTA study was carried out in order to assess whether any of these factors predicted whether an individual would consent to take part in the trial. This chapter will detail the methods and results of the cross sectional study. These findings have already been published in Family Practice, and a copy of the final publication can be found in Appendix Two.

5.2 Methods

The methods of the BAFTA trial are described in chapter 3 and have been published elsewhere.[120] In brief, potentially eligible patients were identified through computer searches for atrial fibrillation supplemented by opportunistic screening of the pulse. An electrocardiograph (ECG) showing AF was required to confirm eligibility for the study. One doctor per practice acted as the local investigator for the study. The research team trained investigators in study procedures and GCP over the four year period (2001 to 2004) that patients were recruited. During this time changes were made both to study procedures and to investigator training. (See Table 10, page 99) These are described in detail in Chapter Six.

Once trained, investigators screened their patients to determine eligibility. The medical records of patients aged over 74 who were found to have ECG confirmed AF were examined for presence of any study exclusion criteria and if the GP was in equipoise as to whether or not they should be treated with aspirin or warfarin after review of relevant risk factors for

stroke and haemorrhage, the patient was invited to attend a study clinic. Eligible patients were sent a patient information sheet and a letter inviting them to see their primary care physician to discuss trial participation. During this appointment, the patient made the decision whether or not to take part in the study.

Table 10: Summary of Changes to the Trial Procedures

Criteria	Date of Change	Detail of Change
Changes to trial procedures	2002	Broadening of inclusion criteria to allow people already on warfarin to be considered
	2003	Assessment process of patients simplified to shorten time from investigator training to patient recruitment and to reduce investigator workload
		Payments to practices changed from payment in advance to payment for work carried out
	2004	Computer searches for atrial fibrillation expanded to reduce need for opportunistic screening, and thus further reduce investigator workload
Changes to training methods	2003	Training sessions reduced from 8 to 5 ½ hours
		New evidence to support study rationale included[137]
	2004	Training sessions reduced to 4 hours
		Good Clinical Practice (GCP) reduced and made more study specific
		More detail on rationale for study
		Sessions made more interactive

This analysis focuses on the 1763 patients from 262 practices in England and Wales who demonstrated that they were willing to consider study participation by attending the study clinic. Both patient and practitioner factors were taken into account. (See Table 11) Data were collected from a variety of sources: information on past medical history and medications were collected from the medical records; disability score (Rankin) was completed by the patients

during the study clinic appointment; practice and practitioner characteristics were collected in a questionnaire completed by each practice on recruitment to the study; data on the year that the practice and the patient were recruited to the study and the number of patients attending a study clinic appointment from each practice were available in the study database.

Table 11: Factors Taken into Account

Patient Characteristics
➢ Demographic characteristics (Sex; age; ethnicity; Index of Multiple Deprivation (IMD) score) ➢ Current medications ➢ Past medical history (diabetes; TIA; stroke; epilepsy; previous myocardial infarction (MI); angina; heart failure; non-rheumatic valve disease; hypertension; AF) ➢ Disability score (Rankin) ➢ Year attended study clinic
Practitioner Characteristics
➢ Demographics (sex; year of full GMC registration) ➢ Size of practice (number of GPs) ➢ Year of practice recruitment to the study ➢ Number of patients attending study clinic

5.2.1 Statistical Methods

Descriptive statistics (patient characteristics and proportions of patients randomised) were carried out using SPSS version 17. The more complex analysis (logistic regression and multi-level modelling) was carried out by the BAFTA study statistician. The effect of patient, practice and practitioner factors on patient consent was explored using logistic regression, univariable for factors considered one at a time and multivariable for factors considered in combination. Further multivariable analysis was conducted using a multi-level mixed effects model.

5.3 Results

1763 people attended the study appointment. Of these, 23 (1.3%) had absolute exclusion criteria and should not have been invited to an appointment to discuss trial entry. These were excluded from this analysis, leaving 1740 patients. Characteristics of these patients can be found in table 12. The mean age of attendees was 81.9 years (range 74-96).

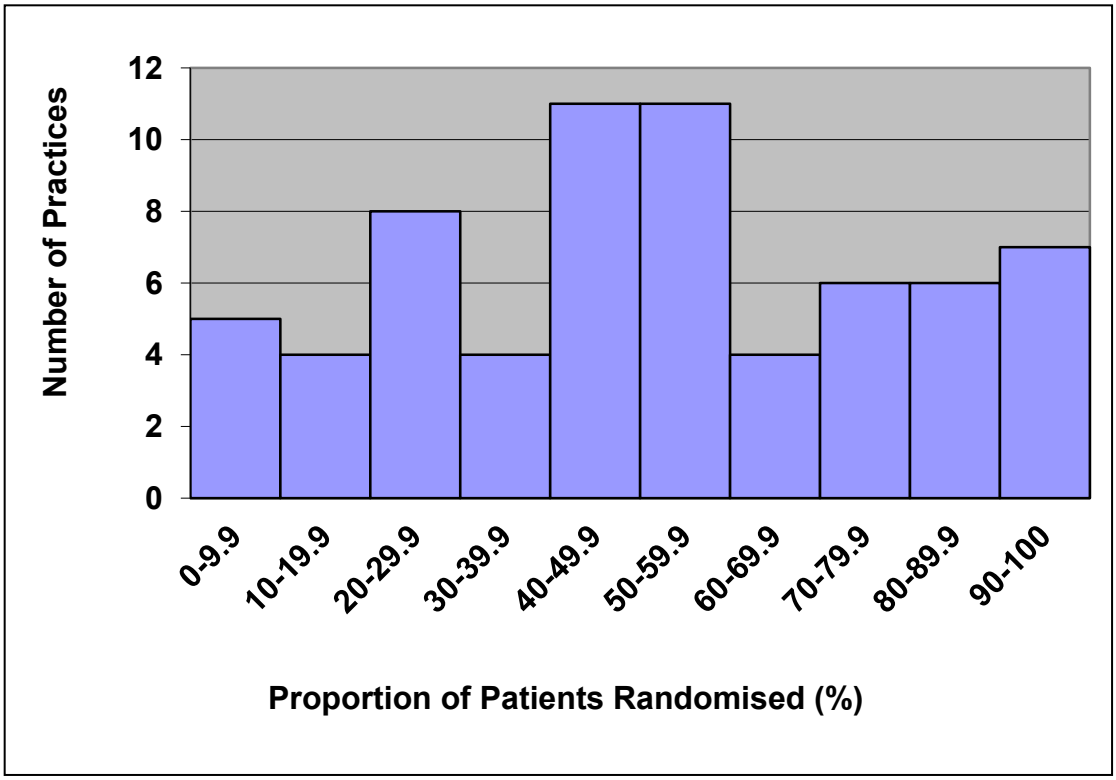
Table 12: Characteristics of included patients (n=1740)

Patient Characteristics		No. (%)ǂ
Randomised*	Yes	973 (56)
	No	767 (44)
Age	75-79	654 (38)
	80-84	676 (39)
	85+	391 (23)
	Not known	19 (1)
Sex	Male	882 (51)
	Female	765 (44)
	Not known	93 (5)
Ethnicity	White	1637 (94)
	Non-white	45 (3)
	Not known	58 (3)
Already on warfarin	Yes	548 (32)
	No	1080 (62)
	Not known	112 (6)
Already on aspirin	Yes	773 (44)
	No	831 (48)
	Not known	136 (8)
History of TIA**	Yes	154 (9)
	No	1489 (86)
	Not known	97 (6)
History of Stroke	Yes	106 (6)
	No	1533 (88)
	Not known	101 (6)
Newly identified AF	Yes	524 (30)
	No	1216 (70)

ǂ Totals may not equal 100 due to rounding
*randomised patients gave full consent to participate in the trial; non-randomised patients gave consent for researchers to have access to their medical records.
**TIA = transient ischaemic attack; AF = atrial fibrillation

973 (55.9%) patients consented to be randomised, although there was a wide variation between local investigators in the proportion of eligible patients who gave their consent (0-100%). (See Figure 7, page 102)

Figure 6: Proportion of Eligible Patients Giving Consent Per Practice*



*Practices who saw fewer than 10 patients at study clinic are not included in this figure

5.3.1 Patient Factors

On univariable analysis, people already on warfarin were more likely to give consent. Patients offered trial entry in 2004 were almost twice as likely to participate as those considered in 2001. Patient socio-economic status also predicted whether or not a patient would consent, although there was not a simple linear association between the quartiles. Patients on aspirin and those with an increased risk of stroke (history of TIA, angina or non-rheumatic valve disease) were less likely to give their consent, as were people aged over 85. There was no significant difference, however, between the two younger age groups. (See Table 12)

On multivariable analysis taking both patient and practice factors into account, patient deprivation and use of aspirin were no longer significant. All other factors that were

significant in univariable analysis remained so with the logistic regression model. (See Table 12, page 105) Patient deprivation was eliminated as it was strongly associated with the number of practitioners in a practice, the number of patients attending a study clinic appointment and the date that the patient entered the study. Use of aspirin was no longer significant because there was a strong inverse association with use of warfarin. With the multi level model, the pattern of effects was very similar to that seen with the logistic regression, with the regression coefficients from the two analyses showing a correlation of 0.95. However, as expected, effects were generally less significant. Previous TIA was no longer significant and the significance of valve disease was marginal (p=0.06). Other factors remained significant.

5.3.2 Practice Factors

On univariable analysis all practice factors, with the exception of primary care physician sex, had a significant effect on a patient's likelihood of giving consent. Patients registered with practices who attended study training during 2004 were almost twice as likely to consent as patients in practices who trained in 2001. Similarly, patients in smaller practices were most likely to consent. There was a clear linear association with practice size, with people being less likely to consent as the number of practitioners within their practice increased. Patients in practices where fewer people attended a study clinic were also more likely to consent. Patients of longer practising primary care physicians (those registered with the General Medical Council (GMC) prior to 1975) were also more likely to give their consent.

On multivariable analysis, the year that the practice was recruited to the study was no longer significant, due to its strong association with the year of patient recruitment. All other factors that were significant in univariable analysis remained so. (See Table 12) With the multi level model, year of full GMC registration was no longer significant.

Table 13: Influence of Patient and Practice Characteristics on Patient Consent (n = 1740)

Patient factors		No. (%) giving consent	Odds ratio (95% CI) from logistic regression	
			Univariable ǂ	Multivariable ǂ*
Sex	Female	443 (58)	1.00	
(No. missing = 93)	Male	530 (60)	1.09 (0.90-1.33)	
Ethnicity	White	913 (56)	1.00	
(No. missing = 58)	Non-white	29 (64)	1.44 (0.77-2.67)	
Age	75-79	385 (59)	1.00	
(No. missing = 19)	80-84	395 (58)	0.98 (0.79-1.22)	1.11 (0.87-1.42)
	85+	193 (49)	**0.68 (0.53-0.88)**	**0.75 (0.56-0.99)**
Index of Multiple Deprivation (quartile) (No. missing = 97)	1 (least deprived)	338 (54)	1.00	
	2	224 (54)	0.99 (0.77-1.26)	
	3	192 (52)	0.97 (0.71-1.19)	
	4	150 (65)	1.55 (1.14-2.12)	
Disability score (Rankin) (No. missing = 60)	0 (least disabled)	173 (54)	1.00	
	1	265 (58)	1.19 (0.89-1.58)	
	2	296 (60)	1.29 (0.97-1.71)	
	3	187 (53)	0.97 (0.72-1.31)	
	4-5	26 (45)	0.70 (0.40-1.22)	
Already on warfarin	No	592 (55)	1.00	
(No. missing = 112)	Yes	381 (70)	**1.88 (1.51-2.34)**	**1.47 (1.13-1.91)**
Already on aspirin	No	527 (63)	1.00	
(No. missing = 136)	Yes	407 (53)	**0.64 (0.53-0.78)**	
Polypharmacy (on 5 or more drugs)	No	559 (55)	1.00	
	Yes	414 (57)	1.07 (0.89-1.30)	
Diabetes	No	844 (59)	1.00	
(No. missing - 95)	Yes	129 (60)	1.06 (0.79-1.42)	
Previous TIA**	No	893 (60)	1.00	
(No. missing = 97)	Yes	80 (52)	0.72 (0.52-1.01)	**0.65 (0.45-0.94)**
Previous Stroke	No	914 (60)	1.00	
(No. missing = 101)	Yes	59 (56)	0.85 (0.57-1.26)	
Epilepsy	No	951 (59)	1.00	
(No. missing = 118)	Yes	7 (39)	0.44 (0.17-1.13)	
Previous myocardial infarction (No. missing = 97)	No	870 (60)	1.00	
	Yes	103 (56)	0.85 (0.62-1.16)	
Angina	No	818 (61)	1.00	
(No. missing = 103)	Yes	155 (52)	**0.67 (0.52-0.86)**	**0.64 (0.48-0.84)**
Heart failure	No	783 (60)	1.00	
(No missing = 100)	Yes	190 (56)	0.83 (0.65-1.06)	

Patient factors		No. (%) giving consent	Odds ratio (95% CI) from logistic regression	
			univariable	multivariable*
Non-rheumatic valve disease (No. missing = 105)	No	905 (60)	1.00	
	Yes	68 (52)	**0.70 (0.49-1.00)**	**0.61 (0.41-0.90)**
Hypertension (No. missing = 97)	No	445 (59)	1.00	
	Yes	528 (60)	1.03 (0.84-1.25)	
AF status**	Already known	683 (56)	1.00	
	New case	290 (55)	0.97 (0.79-1.19)	
Year patient attended study clinic	2001	96 (3)	1.00	
	2002	184 (44)	0.71 (0.50-1.00)	0.70 (0.48-1.02)
	2003	252 (54)	1.06 (0.75-1.50)	1.00 (0.68-1.47)
	2004	441 (66)	**1.75 (1.25-2.43)**	**1.76 (1.18-2.61)**
Practitioner & Practice factors				
Practitioner sex	Female	246 (56)	1.00	
	Male	727 (56)	1.01 (0.81-1.25)	
Year of full GMC registration**	-1975	195 (63)	1.00	
	1976-80	206 (53)	**0.67 (0.49-0.91)**	**0.63 (0.44-0.90)**
	1981-85	195 (54)	**0.70 (0.51-0.95)**	0.70 (0.48-1.02)
	1986-90	238 (62)	0.96 (0.71-1.31)	1.08 (0.74-1.56)
	1991 –	139 (47)	**0.53 (0.39-0.74)**	**0.61 (0.41-0.90)**
Size of practice (no. of GPs)	1-2	98 (75)	1.00	
	3-4	262 (62)	**0.55 (0.36-0.86)**	**1.13 (0.68-1.89)**
	5-6	335 (54)	**0.40 (0.26-0.61)**	0.65 (0.39-1.07)
	7-8	225 (51)	**0.34 (0.22-0.53)**	0.63 (0.38-1.07)
	>8	53 (42)	**0.25 (0.15-0.42)**	**0.40 (0.21-0.75)**
Year of recruitment to study	2001	310 (50)	1.00	
	2002	98 (47)	0.86 (0.63-1.18)	
	2003	262 (57)	**1.31 (1.03-1.67)**	
	2004	303 (66)	**1.95 (1.52-2.50)**	
Number of patients attending	1-5	249 (69)	1.00	
	6-10	286 (49)	**0.44 (0.33-0.57)**	**0.46 (0.33-0.64)**
	11-15	220 (53)	**0.50 (0.37-0.67)**	**0.54 (0.38-0.78)**
	16-20	104 (57)	**0.59 (0.41-0.86)**	0.82 (0.51-1.30)
	>20	114 (56)	**0.58 (0.40-0.83)**	0.77 (0.49-1.21)

ǂ Statistically significant results are given in bold

*Adjusted odds ratio only given if factor significantly associated with likelihood of consent

** TIA = transient ischaemic attack; AF = atrial fibrillation; GMC = General Medical Council

5.4 Discussion

This is the largest study to look at factors influencing patient consent to a multi-centre primary care based RCT. Both patient and practice factors independently predicted whether a patient would consent to take part.

5.4.1 Patient Factors

A number of the patient factors found to be associated with the likelihood of giving consent may reflect general attitudes towards trials, with understanding and acceptance of issues such as randomisation, uncertainty and acceptability of treatment arms playing a part in a patient's decision on whether to participate.[138,139,140] Patients with a history of valve disease, angina or transient ischaemic attack were less likely to give consent. This could be due to the impact of perceived illness severity on trial participation: patients with differing disease processes or illness severities were found to retain different levels of information about trials for different reasons.[139] It is possible that this explains why some conditions predicted the likelihood of consent, while others did not. Alternatively, it is possible that these patients had a strong preference for warfarin as they felt that they had more to benefit from this therapy.[44,141]

Many of the patient factors could also be specific to the interventions (warfarin and aspirin) being tested,4 with patients already on warfarin being more likely to give consent. This presumably reflects the inconvenience and unpopularity of the treatment.[142] People already taking warfarin are perhaps less likely to be deterred from participation because of the need for ongoing monitoring, or because of the uncertainty surrounding the extra risk associated with the drug, than those who have never taken it. Given that how the study is described to a patient can influence participation[43] it is also possible that the way in which warfarin was explained by GPs influenced patients' decisions about whether or not to consent.

The reduced likelihood of older patients (in this case over the age of 85) giving consent has been reported in other studies.[143] The reasons for this are not clear, but it may reflect an aversion to the extra time, expense or tests associated with involvement in a trial. Older people are often carers for their spouses[144] and may feel unable to commit to any further demands on their time. It is possible that as people age they develop more co-morbidities and this means that they are reluctant to risk or complicate their health further. However, this does not seem to be borne out by the research: Petty et al found that patients on five or more drugs (the number of different medications taken by patients is often used as a proxy by researchers for co-morbidity: the higher the number of drugs, the more conditions the patient is expected to have) were more likely to consent than those on fewer medications (OR 1.3, 95% CI 1.1 - 1.5)[143] and the current analysis found that those on five or more drugs were no more or less likely to consent than those who take less (OR 1.07, 95% CI 0.88-1.29). It may be that some potentially 'healthier' people (those on fewer drugs) were actually the people who were reluctant to jeopardise their current health status, and that accounts for these findings.

The year that the patient was invited to enter the study was the most significant patient factor, with a patient approached in 2004 being twice as likely to take part as one approached in 2001. There are several possible explanations as to why there was such a strong association between when a patient was recruited and whether or not they gave consent. It is possible that changes to investigator training methods had an impact on the way in which investigators conducted the consent process (See Table 10, page 99). As discussed in the background chapter, many doctors encounter problems obtaining consent satisfactorily, and changes in training may have helped to alleviate some of these. An individual patient meta-analysis of oral anticoagulants versus aspirin in nonvalvular atrial fibrillation, published at the end of 2002[137] was incorporated into the training sessions in 2003. This helped underline the

uncertainty as to whether the benefits of warfarin outweighed potential harm as compared with aspirin in the study age group. Investigators trained after this date may, therefore, have been more confident that equipoise existed for individual patients,[145] possibly resulting in an increased likelihood that a patient would consent to take part.

There were several changes to trial procedures (See Table 10, page 99) throughout the recruitment period which might account for the increased likelihood of gaining consent over time, though most of these changes will have affected the trial 'upstream' of the consent process. These amendments potentially had a two-fold effect. Simplification of study procedures resulted in a reduced workload for investigators, minimizing the negative impact that a time consuming protocol has on a physician's ability to engage with the research,[4] thus making the project more attractive to them.[146] Changes to both payment methods and study procedures reduced the time between investigator training and commencement of patient recruitment (from approximately four months to approximately two months). Haidich et al demonstrated in a secondary care setting that the longer the gap between study commencement and enrolment of the first patient, the less likely the site is to recruit well.[147] Reduction of the time delay could mean that investigators were more familiar with the trial rationale and protocol than they would be after a lengthy delay. It is also possible that they retained their initial enthusiasm for the study and this translated into improved recruitment. The broadening of the inclusion criteria to allow people on warfarin to be considered may be a partial explanation of the trend observed in patient consent, though it is not clear why there should have been a two year lag before it had an effect. It may be that there was a secular change in patient attitude, either to trial participation in general or the value of warfarin in particular over the study period. Warfarin use has become more common in older people over time,[148] and this may have influenced willingness to participate.

5.4.2 Practice and Practitioner Factors

In this study a higher proportion of patients from smaller practices gave consent than from larger practices. As discussed in chapter two, practitioners can be uncomfortable describing personal equipoise and the randomisation process and will often emphasise aspects of the trial that they expect patients to understand more easily.[149] These difficulties may be mitigated in smaller practices where continuity of care is more likely,[150] and physicians can get to know their patients better, giving patients a feeling of security[151] and the primary care physician a better understanding of[152] and increased feeling of responsibility towards their patient.[118] This enables them to be both more selective about which patients they invite, and more confident that the informed consent discussion will have no detrimental effect on the doctor/patient relationship.

This study also found that older GPs were more likely to obtain consent than younger GPs, although there was not a simple linear relationship with age. The effect of age may reflect a number of factors, including variations in consulting style or differing attitudes to warfarin. It could be that older GPs have a longer term relationship with their older patients, and this builds the trust that facilitates the consent process.[153] Older doctors are seen to be more willing to listen and more reassuring than younger doctors, and are viewed more positively by older patients:[90] these perceptions may help to account for this finding.

5.5 Strengths and Limitations

The patients in this analysis were all considered eligible for the study by their primary care physician and all attended a clinic appointment, so were not averse to trial participation per se. Therefore, the factors considered here impact directly on the process of obtaining consent, rather than on other parts of the patient pathway leading to trial participation, such as willingness to attend, or physician decisions about eligibility. Another strength is the large

size, and the high degree of data completeness, with over 90% data completeness (worst data item was prior aspirin use, with 7.8% missing data).

There are some weaknesses to this analysis. Although it demonstrates that a wide variety of factors influence recruitment, it does not allow us to understand how or why these characteristics have such a significant effect. It is based around a single trial, so may be difficult to generalise to other primary care trials. However, there are findings here that are of general interest. The effect of practice size and the impact of year of recruitment are unlikely to have been primarily related to the nature of the trial interventions. Furthermore, as the way that study treatments are described to a patient influences whether or not they are willing to take part,[43] it is possible that even study specific factors (i.e.acceptance of the trial drugs) were influenced by how the investigator conducted the consent process.

5.6 Implications for Future Primary Care Based RCTs

The two fold difference in the likelihood of whether or not a patient would give consent over the time course of the study, having adjusted for the influence of other patient and practice factors, suggests that the conduct of a trial can have a dramatic effect on patient recruitment. It is possible that changes made to investigator training, study procedures and payment methods account for this finding. As the analysis only considered patients who were eligible for the study and who went through the informed consent procedure, the changes must have affected either the type of patients attending this appointment, or what was said to them during the consent process. The evidence base for how to train investigators and conduct trials in primary care is poor.[74] This analysis suggests that research into this area could yield important benefits in terms of enhancing recruitment to future studies.

Given the strong association found between year of recruitment and consent, it was decided to analyse in greater detail the secular trends in recruitment to BAFTA, and observe to what extent these were associated with changes in the conduct of the trial. This analysis is described in the next chapter.

Chapter 6: Trends in the Recruitment of Patients to BAFTA

As discussed in Section 4.2.2, it is not clear from the literature whether or not trial conduct can influence the recruitment outcome to a trial. This chapter will examine whether changes to BAFTA trial procedures and protocol amendments were associated with changes in patient recruitment.

6.1 Background

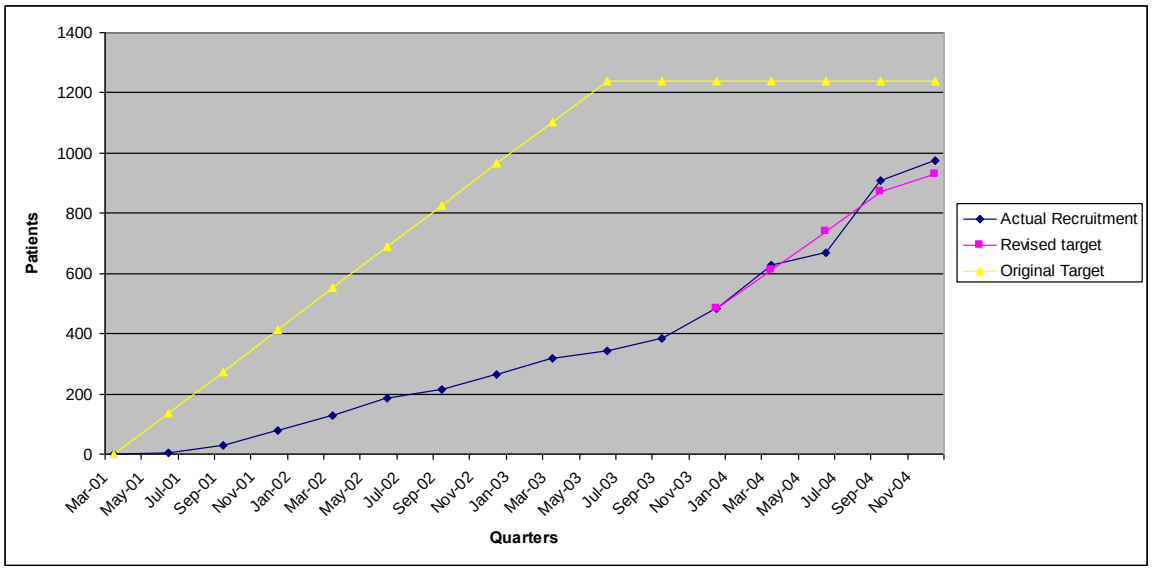
Although there is a growing body of evidence that indicates that trial conduct can influence the success or otherwise of patient recruitment (See Chapter 2), there is a contrasting argument put forward by Haidich et al that trials that initially fail to achieve recruitment targets cannot implement design changes that will improve patient recruitment. These authors undertook an analysis that examined recruitment patterns to 77 human immunodeficiency virus (HIV) efficacy trials. They found that the pace of accrual within the first two months of recruitment was associated with the likelihood of a trial ultimately reaching its targets (88% of very rapid early enrolling trials achieved targets versus 20% of slow early enrolling trials, $p < 0.001$). They also found that none of the included studies showed a marked acceleration of accrual over time, despite the fact that restrictive entry criteria were often relaxed in an attempt to boost recruitment. They concluded that, as even extensive protocol changes were unlikely to accelerate recruitment, the initial pace should be used to decide on the feasibility of completing an under performing trial and early termination due to futility should be seriously considered.[128]

One disadvantage of the analysis carried out by Haidich et al is the fact that the included trials were all looking at HIV. The authors acknowledge that this field has its own peculiarities, for example, rapidly expanding therapeutics or changes in the course of the epidemic affecting the pool of eligible patients, and that this may have influenced their findings. However, they posit that other diseases with steadier prevalent patient pools may have even more predictable enrolment patterns, therefore making early recruitment rates an even stronger indication of future trial success.[128] Unfortunately, there were no articles that examined trials that were initially failing to achieve targets but were ultimately successful;[2] a study of this nature would be useful for three main reasons:

1. It may be possible to identify protocol or procedural changes that influenced recruitment without having to consider complicating factors such as different disease types or differing patient populations;
2. It could add information to the current body of literature about the most appropriate way to approach recruitment from trial set up, therefore reducing the need for potentially costly or time consuming changes throughout the life of the trial;
3. It would provide useful evidence to counter the assertion of Haidich et al that the initial recruitment rate should be used to glean the eventual fate of a trial.

The BAFTA study is an example of an ultimately successful trial where initial recruitment did not predict the overall recruitment rate (see Figure 8, page 113). Analysis of BAFTA recruitment as described in the previous chapter demonstrated that patients in the final year of recruitment were almost twice as likely to participate as those in the first year, suggesting that changes introduced during the course of the trial influenced recruitment.

Figure 7: BAFTA Recruitment Targets



In order to address the question of whether the increase in recruitment over time was due to an increase in the size of the study population as a result of expansion of the number of active sites, or due to changes in study design and conduct, this chapter will describe the actions taken to improve accrual to the BAFTA trial and will examine recruitment patterns to try to identify which of the changes made to the design and conduct of the study were most closely associated with recruitment rates. Although this is an observational study and cannot therefore determine cause and effect, it is hoped that the findings will: provide a useful addition to the existing body of literature; air a note of caution to funders and Trial Steering Committees who may consider the findings of Haidich et al when deciding the fate of under-performing trials; and provide a springboard for future research into trial conduct. The findings from this chapter have been published in the Family Practice journal: the full published article can be seen in Appendix Three.

6.2 Methods

6.2.1 Recruitment Processes

As detailed in section 3.4.11, each participating practice nominated one GP to act as local investigator, and one practice nurse (PN) to assist the GP with the identification and recruitment of patients. In summary, the research team trained all nominated practice staff in study procedures and GCP: after attending training, practices were responsible for the identification and recruitment of potentially eligible patients. Practice nurses carried out an electrocardiogram (ECG) on all patients with an AF diagnosis in their medical records, or who were found to have an irregular pulse during opportunistic screening. When AF was shown on the study ECG, GPs examined patients' medical records to establish the presence of study exclusion criteria. If the GP was in equipoise over whether to treat a patient with aspirin or warfarin then the patient was invited to an appointment to discuss trial participation. (See Figure 4, page 84) Patient recruitment was carried out over a four year period (2001-2004), but it became apparent within the first six months that the study was failing to recruit enough patients: accrual rates were poor.

6.2.2 Actions Taken to Improve Recruitment

Over the recruitment period a variety of changes were made in an attempt to improve accrual. These included: revision of inclusion/exclusion criteria; procedural changes to reduce primary care workload and time to recruitment; expansion of the number of active sites; and a different approach to the recruitment and retention of practices. (See Table 13, page 115) Further details about the amendments are given below.

Table 14: Changes to Trial Procedures and Protocol amendments

Protocol changes

Change number	Date introduced	Problem	Change	Procedure prior to change	Procedure post change	Expected Impact
1	2002	Lower than expected prevalence of AF on study ECG	Amendment to inclusion criteria 1 Allows patients to be potentially eligible if have ECG diagnosis of AF in records but sinus rhythm (SR) on study ECG	All patients ECG'd prior to determining eligibility and ineligible if SR on study ECG	Patients with ECG in records (within 2 years) showing AF now potentially eligible. Only patients consenting to participation have study ECG, allowing categorisation into AF or paroxysmal AF	Reduction in investigator workload Increased number of potentially eligible patients
2	2002	Higher rate of patients already taking warfarin than expected from the literature	Amendment to inclusion criteria 2 Broadening of inclusion criteria to allow people on warfarin to be considered	Patients on warfarin were ineligible.	No change to procedure.	Increase in numbers eligible.
Procedural changes						
3	2002	Intensive practice workload	Reduced workload 1 ECGs only carried out on potentially eligible patients	ECGs carried out on all patients with AF on computer searches and patients with an irregular pulse	ECGs now only carried out on potentially eligible patients	Decreased workload

Change number	Date introduced	Problem	Change	Procedure prior to change	Procedure post change	Expected Impact
4	2003	Intensive practice workload	Reduced workload 2 Data on past medical history and medications only collected on potentially eligible patients	Data collected on all patients with AF	Practices no longer search medical records for detailed data for patients who are ineligible for the trial	Decreased workload
5	2004	Intensive practice workload	Reduced workload 3 Evidence of AF in patient records used to determine eligibility, patients only have ECG once they have consented to participation	All potentially eligible patients received a study ECG prior to randomisation	Practices look for evidence of AF in the records when determining eligibility for the study. Patients then invited to participate and receive an ECG if they consent to randomisation	Decreased workload
6	2004	Intensive practice workload/ recruitment timeframe (recruitment closed September 2004)	Reduced workload 4 Practices no longer carried out opportunistic pulse screening	All patients without AF on computer searches would have their pulse screened to identify potential new cases of AF	Opportunistic screening no longer carried out. Incident cases of AF could still be considered	Decreased workload and shortened time to complete recruitment process
7	2004	New trial team approach to site retention		Once trained, the study team would endeavour to keep each site as participants, offering help and support where appropriate	Under performing practices or sites who were unsure about their ability to carry out the work within the required time were simply allowed to withdraw	Enthusiastic successful practices to remain active, ensure optimal recruitment and optimal allocation of study team resources

6.2.2.1 Revision of Inclusion/Exclusion Criteria

Protocol Amendment One

One of the issues identified as contributing to poor recruitment was the higher number of ineligible patients than was anticipated. As shown in table eight, one of the exclusion criteria at the start of the recruitment period was if a patient was already taking warfarin. It was estimated from the literature that 17% of the prevalent AF population over the age of 74 would be taking warfarin, and it was assumed that it was appropriate for these to be on a potentially dangerous treatment despite the lack of evidence to support this, because they were usually patients who had co-morbidities that further increased their risk of stroke. In reality, 34% of patients in the target population were on warfarin prior to the study. This situation effectively doubled the number of ineligible patients from the prevalent AF population, so some analysis of data collected from participating practices was carried out. This analysis demonstrated that many people were taking warfarin who were not at extra risk of stroke, and so the balance of risk and benefit for them was still unknown. Therefore, it was appropriate that they were also eligible for study inclusion and in 2002 the protocol was amended accordingly.

In addition to increasing the pool of eligible patients, this protocol amendment had two further potential advantages:

1. It reduced the level of complexity for the practice staff carrying out the trial;
2. It reduced the time from practice involvement to patient recruitment.

Although people on warfarin were originally ineligible, practice nurses were still asked to invite them to the initial clinic where an ECG was carried out and pre-baseline data was

collected: this would allow generalisability of trial results to be examined. Informal discussions with PNs revealed that they often found this confusing, and so they had a tendency to invite all their warfarin patients to the ECG clinic before they considered any who were potentially eligible. While this approach reduced the complexity of the study for practice staff (which may contribute to improved recruitment, as discussed in the background chapter), it also meant that there was a long time lag between the commencement of practice involvement and the recruitment of their first patient, resulting in slower than anticipated accrual. It was hoped, therefore, that this amendment would improve recruitment from a number of angles.

Protocol Amendment Two

Another issue that was felt to be contributing to poor recruitment was that of Lasagna's Law.[115,116] Estimates for the number of people expected to have AF were taken from the literature; as is often reported in articles looking at recruitment problems, the disease prevalence seemed to be far lower in reality than was expected. In the case of BAFTA, patients were only eligible if their study ECG showed AF: it was found that many study ECGs showed sinus rhythm (SR), despite the fact that they had a diagnosis of AF in their medical records. It was felt that this anomaly was caused by a higher than expected prevalence of paroxysmal AF (where patients switch between AF and SR): patients were only eligible if they happened to be in AF at the time of their ECG. The protocol was amended to allow inclusion of paroxysmal AF patients. Post amendment, patients with an ECG in their medical records (within two years) showing AF were potentially eligible and only those who consented to study participation were given a study ECG. This allowed categorisation of patients into constant AF and paroxysmal AF groups.

6.2.2.2 Procedural Changes

A number of procedural changes were made that were intended to reduce the workload to practice staff.

Change One (changes to the number of patients requiring a study ECG)

PNs were initially asked to carry out ECGs on all patients who had AF on computer searches, as well as on all patients who were found to have an irregular pulse as part of the opportunistic screening programme (Section 3.4.7), regardless of whether or not they were potentially eligible. Again, this was intended to allow generalisability of the trial to be examined. However, this represented a massive time investment on the part of the PNs. It was felt that they were spending time on the collection of data on ineligible patients that would be better spent on actual recruitment. Therefore, in 2002, nurses were asked to only carry out ECGs on people who did not have any of the study exclusion criteria.

Change Two (changes to the data collected on ineligible patients)

Initially, data on medical history and medications were collected on all patients with AF. This necessitated detailed searching of the medical records and the completion of study Case Report Forms (CRFs) for large numbers of patients. Again, this was done to allow the discussion of study generalisability, and again, it was decided that nurse time would be better spent focussing on eligible patients. Therefore, in 2003 nurses were asked to collect this information on potentially eligible patients only.

Change Three (further changes to the number of patients requiring a study ECG)

Despite the changes already implemented, all potentially eligible patients received an ECG prior to study inclusion and this still represented a heavy workload for practices. In 2004, further changes were made to address this. Instead of carrying out an ECG on all eligible

patients, nurses were instead asked to search medical records for sufficient evidence of a diagnosis of AF. This evidence could either be an ECG that had been carried out within the preceding two years, or a hospital consultant letter that referred to an ECG showing AF, also within the preceding two years. ECGs were then only carried out on patients after they had consented to study participation. This change represented not only a significant reduction in workload, but also had the added benefit of minimising the delay between a practice becoming active and recruiting their first patient.

Change Four (changes to the opportunistic screening programme)

All patients aged 74+, without a diagnosis of AF in their records were part of the opportunistic screening programme for the study. Each patient had a flag attached to their records (either electronic or paper as appropriate to individual practices) reminding all clinical staff to take their pulse during a routine consultation. As this needed to be done only once for each patient, once the pulse had been taken the request was removed from the notes. All patients having an irregular pulse on this examination then received an ECG to determine eligibility for the trial. This was another time consuming process for practices. Practice staff had to add reminders to patient medical records in all practices where paper notes were routinely used during consultations, and they were also responsible for ensuring that processes for following up patients with an irregular pulse were in place. Although patient recruitment was due to close in September 2004, practices were still being trained and becoming active in April. In order to enable them to complete recruitment within these tight time frames, these practices no longer carried out the opportunistic screening programme, although incident cases of AF were still eligible for inclusion.

6.2.2.3 New Research Team Approach to Site Retention

Recruitment and training of sites is a time consuming and costly part of the trial process, and as discussed in section 3.3.1, is potentially one of the most problematic areas of recruitment for primary care based trials.[65] Initially, the BAFTA team put significant resources into ensuring that all trained sites would remain active participants. Support to resolve queries or concerns was given, and where appropriate and possible, practical assistance in the form of administrative help or nurse time was offered. The research team worked closely with under-performing sites, or those expressing reservations about their ability to commit to the level of work involved, in an effort to enable them to recruit. However, as the number of sites increased and became more geographically diverse, and the time frames for completion of recruitment became increasingly short, a decision was taken that these practices would simply be allowed to withdraw. This allowed enthusiastic and successful practices to remain active, ensuring optimal recruitment and the most appropriate allocation of study team resources.

6.2.2.4 Changes to the Training Sessions

Changes were made to the timing and content of the training sessions over the four year recruitment period. Initially, a GP and PN from each site were required to attend a full day training session. The morning was spent discussing generic trial issues, for example, GCP, trial rationale, ethics: in the afternoon, GPs and PNs were divided into small groups and specific trial procedures appropriate to their role were discussed. Each year, changes were made to the sessions and they became increasingly streamlined. For example, GCP sessions, although covering the crucial elements, were much more study specific; less time was spent describing the study manual and study Standard Operating Procedures (SOPs) as these areas were incorporated into the more practical afternoon sessions. By 2004, the training sessions were condensed to a half day session which still incorporated important generic issues such as GCP and trial rationale, but were more focussed on the practicalities of carrying out the

research. This made it easier for practice staff to attend the sessions: releasing two members of staff from the practice for half a day is much easier for sites to achieve than releasing them for a full day. Full details of the topics covered during training can be found in the example training session agendas in Appendix One.

6.2.3 Statistical Analysis

This analysis was performed to address the question: was the increase in recruitment over time simply due to an increase in the size of the study population (i.e more practices were taking part), or due to the changes in the design and conduct of the study? To explore this, analysis was undertaken to look at whether the recruitment rate per population available varied over time in line with the observed increase in recruitment. If the increase in recruitment was potentially due to changes in how patients were recruited, this would be associated with an increase in recruitment rate per 1,000 population.

The recruitment phase of the study was divided into 3 month periods. For each quarter, only data from active practices (those who had reviewed their patients for eligibility or had invited two or more patients to attend a study clinic during the period) were included. For each quarter, the number of patients enrolled into the study was calculated. The recruitment rate per 1000 patient population was also calculated; the denominator was the population of patients aged 75+ in active practices. In order to identify whether there was a seasonal effect on recruitment, the effect of quarter on recruitment was also examined. 95% confidence intervals were calculated to identify whether there were any significant increases/decreases in recruitment rates. The analysis was carried out using SPSS version 17.

6.2.3.1 Further Analysis for Publication

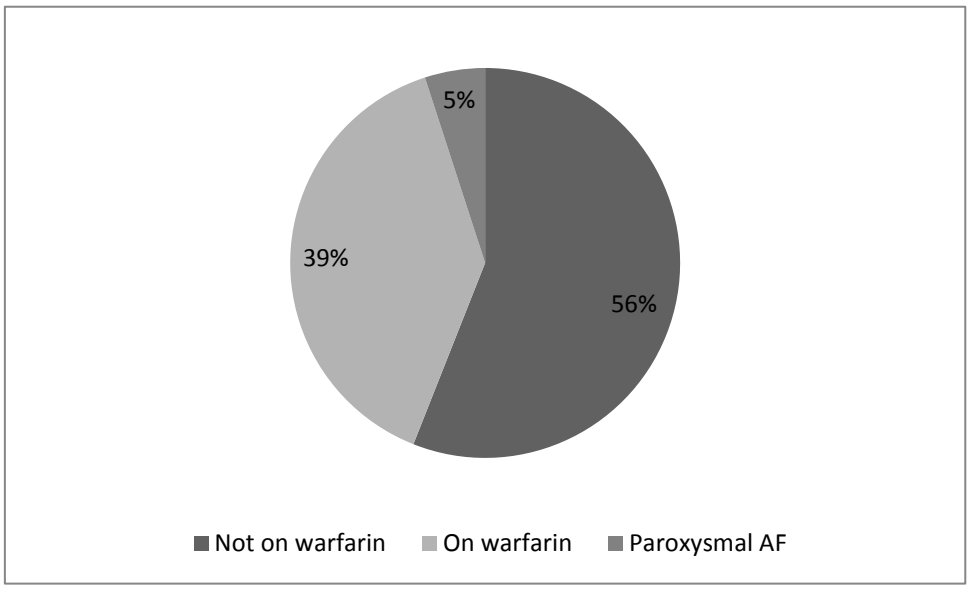
In order to determine whether there was a significant change in recruitment rate, a conducted change point analysis with the Moving F statistic using the first seven quarters as the baseline

sample and a moving average of three quarters was carried out.[154] This was done at the request of peer reviewers to enable publication and was carried out by one of the BAFTA study statisticians.

6.3 Results

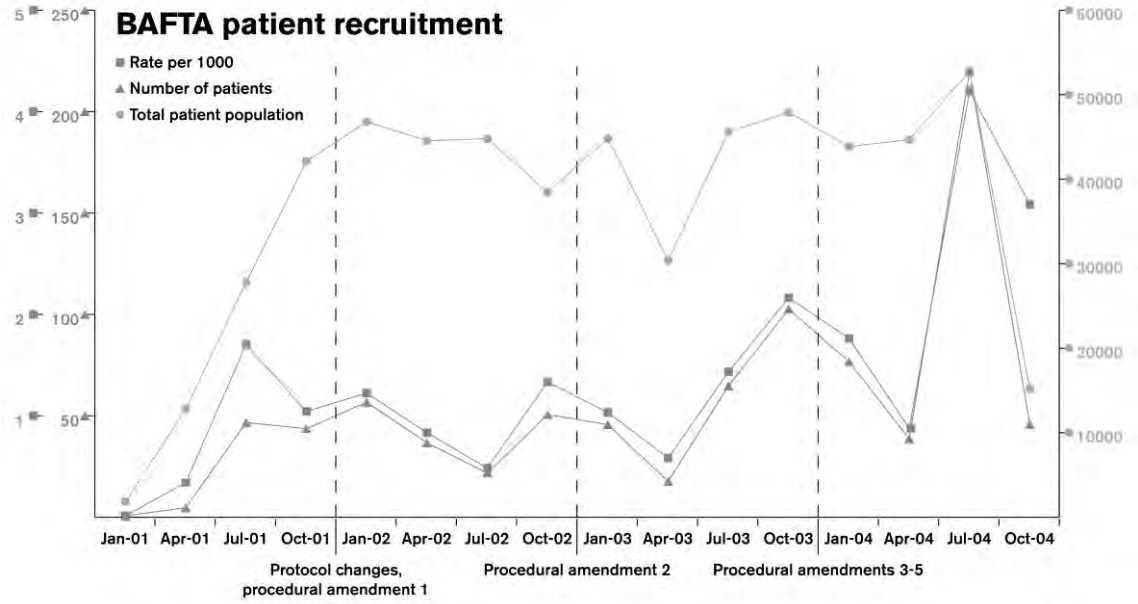
A total of 535 practices attended study training sessions, with 330 (62%) continuing through to active participation. Of those, 257 (78%) sites saw at least one patient at a randomisation clinic appointment and 234 recruited one or more patients. The revised target of 930 patients was exceeded, with 973 people recruited into the trial. An average of 65 patients were recruited per quarter (range 4-219). The overall recruitment rate per 1000 study population was 4.7 patients. The average rate per practice was 5.5 patient per 1000 (range 0-66.7). This is higher than the overall average as it reflects the number of smaller practices that recruited a high proportion of their patients. Protocol amendments accounted for 44% of patients recruited. (See Figure 9)

Figure 8: Proportions of Recruited Patients as per their Status at Baseline



Recruitment fluctuated during the recruitment period with a number of changes to the numbers recruited. (See Figure 10) The last half of 2003 saw a large increase in recruitment, but this was dwarfed by a bigger rise in the last six months of the study, which followed the introduction of a number of procedural changes (See Table 10, page 99). In general, the pattern of changes in numbers recruited per quarter was closely matched by changes in recruitment rate per 1000 population. (See Figure 10) Broadly speaking fluctuations in the size of the total study population also reflected these recruitment patterns, with higher recruitment attained in quarters with a larger total study population and vice versa. However, the large increase in both recruitment numbers and rates in the last six months of the study was not mirrored by a similarly large increase in the total population available.

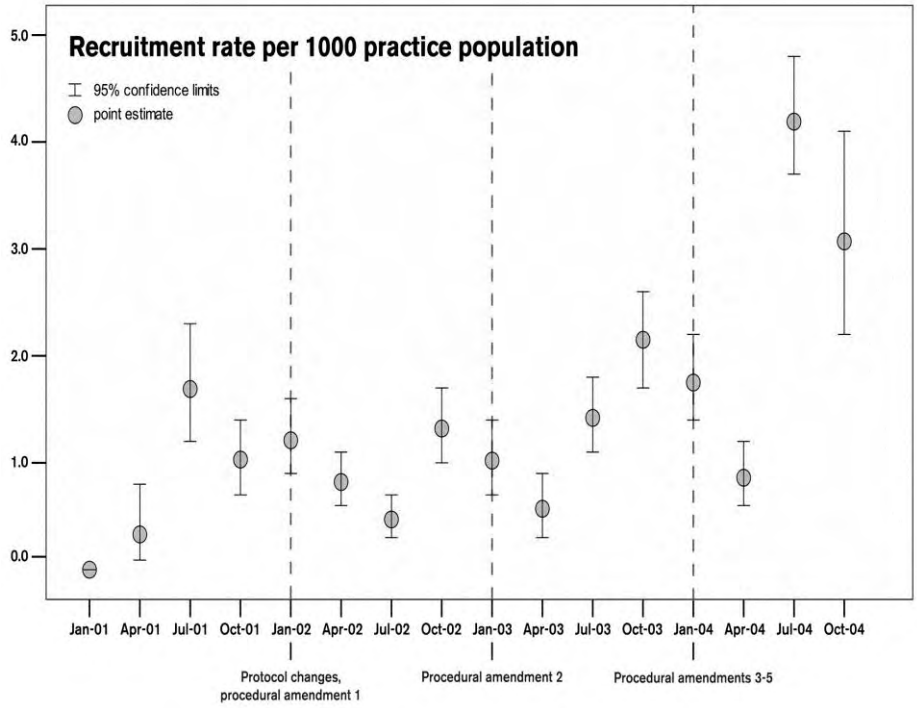
Figure 9: BAFTA Patient Recruitment Patterns*



*see table 14 for full details about protocol changes and procedural amendments

95% Confidence Intervals demonstrated a number of statistically significant increases in recruitment, in quarter 3 2001, quarter 4 2002, quarter 3 2003, and most noticeably in quarter 3 2004. (See Figure 11, page 125)

Figure 10: Confidence Intervals around Recruitment rates*



O point estimate

I 95% confidence limits

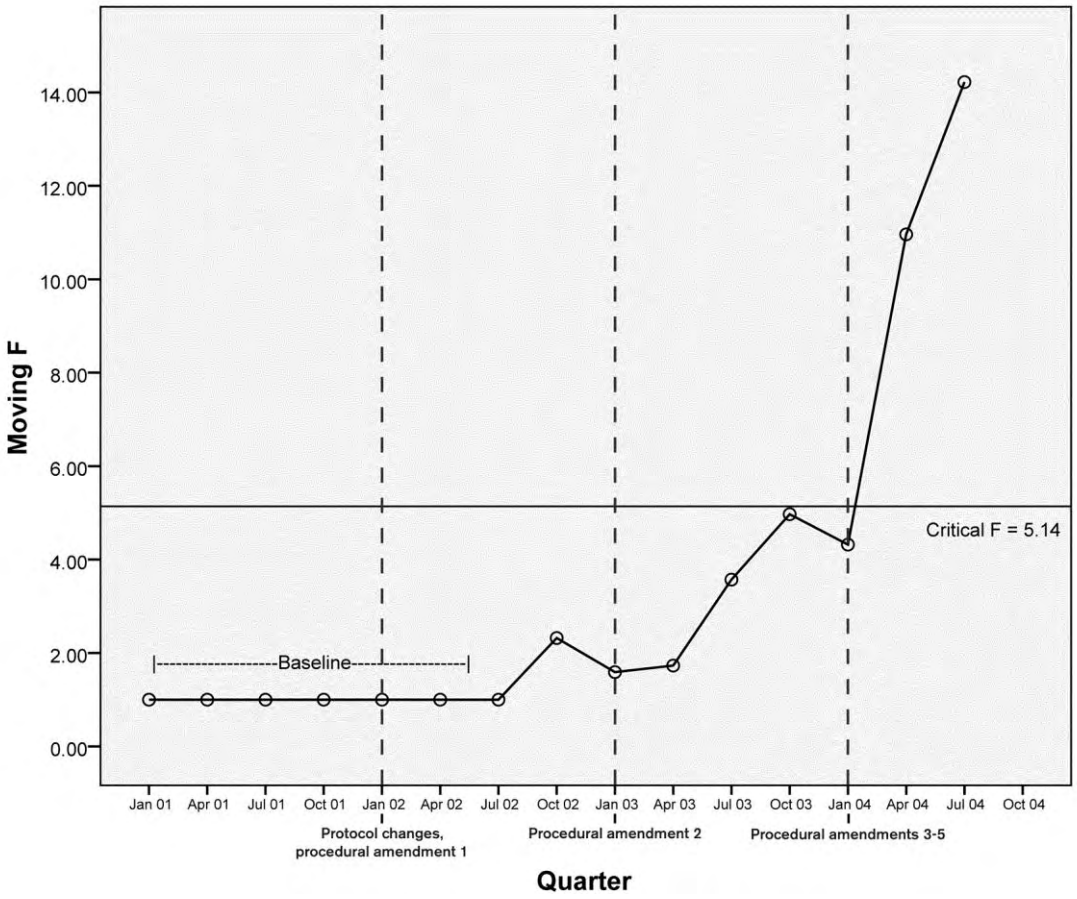
*see table 14 for full details about protocol changes and procedural amendments

6.3.1 Further Analysis for Publication

When published, peer reviewers requested that some further analysis was carried out. BAFTA study statisticians calculated the Moving F statistic. The Moving F is calculated as the moving average of squared deviations about the series model in ratio to the baseline residual mean square. A change is identified when the Moving F crosses the critical F.

Analysis using the Moving F statistic demonstrated that there was a significant increase in recruitment rate ($p<0.05$) in the last six months of the study. (See Figure 12, page 126)

Figure 11: Moving F Statistic*



*The horizontal reference line indicates the critical F(2,6,0.95)=5.14.

6.4 Discussion

This study found that the increase in recruitment in the last 6 months of the study was associated with a significant rise in recruitment rate per 1000 population, rather than merely with an increase in the overall size of the study population. Inclusion of more sites to increase the total study population is an obvious way of improving recruitment. As discussed in the background chapter, it is an approach that is often advised in the literature, and is something that trialists often utilise.[3,18,29] However, this analysis indicates that recruitment to BAFTA was affected more by factors influencing the proportion of eligible patients participating than it was by the expansion of the number of recruiting sites.

The protocol modifications in BAFTA had mixed success. Broadening of inclusion criteria had no immediate impact on recruitment; both amendments to eligibility criteria were carried out early in the recruitment process and were not associated with a noticeable increase in recruitment. However, when considered overall, these changes did make a significant contribution to the number of patients included in the study, as 44% of patients would have been ineligible prior to the modifications (See Figure 9, page 123). These findings demonstrate the importance of careful consideration about inclusion/exclusion criteria during the protocol design phase: it would be better to set these parameters optimally from the outset. This can be difficult to achieve, as prevalence estimates are usually gleaned from the literature and often do not reflect reality. Pilot trials may allow recruitment estimates for the main trial to be based on real prevalence figures and therefore reduce the number of trials failing to reach expected accrual targets.

This finding also has implications for bodies who are considering the fate of failing trials. Haidich et al suggested that even extensive protocol amendments fail to achieve impressive acceleration in recruitment rates; BAFTA recruitment demonstrates that, while the protocol changes may not result in immediate large increases in accrual, overall they have the potential to contribute a significant proportion of study patients. Funding bodies or Trial Steering Committees need to allow sufficient time for the amendments to filter through before deciding on the feasibility of a study.

As discussed in section 6.2.2.2 a number of procedural changes to reduce investigator workload were introduced (See Table 10, page 99). Figure 12 (page 126) demonstrates that early changes did not seem to impact on recruitment although changes introduced in 2003 were followed by a noticeable but not statistically significant increase. The 2004 amendments,

however, were associated with a significant increase (See Figure 12, page 126). Unfortunately it is not possible to determine from this analysis whether this increase was a direct result of the procedural changes that were implemented that year: it could have been a result of the cumulative effect of the alterations that took place over the whole recruitment period.

There may also be other explanations for the observed increase in recruitment. In 2004 a new approach to site retention was adopted by the research team, with underperforming or overstretched practices simply withdrawing from participation (See Table 10, page 99). Remaining practices were likely to have been more interested in the study question or more able to incorporate the extra workload into practice, and it is possible that this translated into more successful recruitment. Furthermore, these practices had tight timeframes within which to complete recruitment, so they may have given the study a higher priority.

It is possible that factors extrinsic to the trial might have been responsible for the observed increases. In 2002 an individual patient data meta-analysis was published which helped underline the uncertainty surrounding the benefits and harms of aspirin versus warfarin in the over 75 age group.[137] This new evidence was incorporated into investigator training in 2003. This may have made GPs more confident about the treatment uncertainties and therefore more comfortable with explaining equipoise to individual patients. How a study is explained to a patient has been shown to impact on their willingness to participate,[43] so better acceptance of the study question by investigators may lead to more patients giving consent.

The increased recruitment rates could also be a result of changes in patient attitudes, either to warfarin or to participation in trials in general. Warfarin use in older people has increased

outside of trial settings;[148] increased general acceptance of one of the study drugs may account for their increased willingness to participate.

6.5 Strengths and Limitations

One strength of this analysis is that it demonstrates identifiable time points in the recruitment period which can be related to both protocol and procedural changes. Unfortunately it is not possible to determine what aspects of the steps taken to improve recruitment were actually responsible for the changes in recruitment. The large jump in recruitment seen in 2004 may have been caused by any one of the interventions described, or by a combination of all of them. Nevertheless, this analysis does provide evidence that it is possible to significantly improve recruitment rates without simply recruiting more centres, and gives an insight into ways in which this may be achieved. It is difficult to generalise from the particular (i.e. recruitment of older people to a trial of atrial fibrillation) to the general (i.e. recruitment to primary care trials across different diseases and ages). Despite this, the lessons learnt, for example with regard to workload minimisation and simplification of study protocol, add weight to the existing body of literature and could be considered by investigators designing other trials.[90,155]

6.6 Implications

The findings suggest that the conduct of a trial is a vital consideration if accrual targets are to be reached. Minimisation of investigator workload seems to be important and care should be taken to ensure that only relevant data are collected. For example, data collection on non-eligible patients to consider generalisability issues diverts resources from patient recruitment. Whilst generalisability is important to the external validity of a trial, it is vital to ensure that the focus of effort is on patient accrual; data collected to ensure generalisability must be secondary to this aim. Expanding the number of active sites, while logical, is not necessarily

the most effective way of improving recruitment. It may be more useful for trials to consider whether other approaches would be more appropriate before investing time and money in expansion.

Care should also be taken when using early recruitment data to predict overall recruitment or to determine the continued feasibility of a study[128] since initial patterns may not account for the potential success of protocol changes. Therefore, one very important implication of these data is how funders of research interpret initial recruitment data. If the funder had not shown flexibility in extending the trial, BAFTA could have failed. Given the major clinical impact of the study, this would have been unfortunate. Reasonable time for protocol amendments to take effect is needed and funders need to balance reasonable desire to stop a trial where recruitment targets seem futile with the cost to society of never answering the research question. Prospective studies to test the impact of interventions on recruitment rates would benefit future RCTs.

Chapter 7: Interview Study Methods

This chapter introduces the interview methodology, describes participant selection and recruitment, then details the development of the topic guide and conduct of the interviews. It continues with description of how the analysis was carried out, and concludes with an explanation of how the results are presented.

Ethical Approval

Ethical approval was obtained for this study as an amendment to the main BAFTA study approval, from the West Midlands Multi-centre Research Ethics Committee (Ethics Reference: MREC/99/7/57a). Approval was also gained from all relevant Primary Care Trusts.

7.1. Semi-structured Interviews

While designing the project, the use of focus groups instead of individual interviews was considered. The decision to use semi-structured interviews was discussed in detail in Chapter four. During the interviews, a topic guide was used to guide the interview, but the main aim was to use the prompts to gain a detailed understanding of the interviewee's perspective. An audio recording was made of the interview, which was later transcribed verbatim by the interviewer or an administrator. The first four interviews were transcribed by the researcher. Repeated listening and verbatim transcription of these interviews enabled the interviewer to become immersed in the data and identify tentative explanations and note unexpected topics for exploration in further interviews.

7.2. Recruitment of Interview Participants

This section will look at the sampling strategy used in this project, and will describe how the participants were recruited.

7.2.1. Sampling Strategy

The intention initially was to use purposive sampling to identify participants. Purposive sampling is defined by Pope and Mays as a deliberate choice of respondents representing theoretically important groups of subjects.[156] This approach is used to gain a wide range of perspectives, as opposed to a statistically significant sample that is representative of the population. It allows selection of specific participants based upon the findings of previous research. The aim was to include GPs representing a range of characteristics previously shown to be associated with recruitment to BAFTA (See Table 14, page 134). However, this approach can be time consuming: GPs have to be selected and invited, non-responders need to be chased and those declining the offer have to be replaced by GPs with similar characteristics, thus starting the whole process again. It was considered vital that GPs were interviewed before the BAFTA results were published because some of the questions related to their thoughts about the study question or interventions. It was felt that knowledge of the trial results could change the responses to these questions. The BAFTA results were fast tracked and were due to be published in May 2007. Therefore, there was only a two month window in which to carry out all the interviews; it became apparent that this approach to GP recruitment would not allow enough time for them to be completed. Therefore, a more pragmatic approach to recruitment was taken.

The actual process of selecting and inviting GPs is described in more detail in section 7.2.2. This section will focus on the aims of the sampling, while the extent to which the aims were

achieved will be discussed in section 8.3. The sample was taken from GPs who carried out randomisation clinic appointments with patients who were eligible for the BAFTA study. As informed consent was carried out during the randomisation clinic appointment and one of the aims of this study is to examine the GP experience of taking consent, GPs who had not carried out one of these clinics were excluded from the sample. Practices where it was known that the recruiting GP was no longer working there were also excluded. It was considered important to include GPs with varying levels of recruitment success in the sample, as the aim was to identify whether different attitudes or experiences between those who were more or less successful at gaining consent existed. Therefore, proportions of the eligible patients (i.e. those who attended a randomisation clinic appointment) who gave consent were calculated and split into four recruitment groups (See Table 14, page 134); GPs were sampled from each group.

Most of the sampling criteria were those previously found to be statistically associated with gaining consent (See Table 14, page 134). Year of GMC registration was used as a proxy for GP age, as age was not available in the study database. Year of registration was taken from the CVs provided by the GPs on study entry; where this was missing the information was collected from the GMC website.[157] Practice size was calculated using the number of GPs working in the practice; this was available in the BAFTA database. In order to ensure that the very small and very large practices, as well as a range of sizes in between these extremes were represented, practices were divided into three groups (See Table 14, page 134). Year of study training was also included in the sampling framework. Although this was not significant in previous analysis, it was closely associated with the year that a patient was recruited to the study, which was a highly significant patient level factor. Year of practice recruitment would therefore allow exploration of whether there were any time dependent effects on GP attitudes or experiences. Practice recruitment and training for BAFTA was carried out over a four year

period (2001-2004); practices were selected to ensure that each recruitment year was represented. Practices trained in 2001 and 2002 were grouped together for sampling, as there were relatively few practices trained throughout 2002.

One further characteristic was included in the sample: practice location. Although this was not included in the previous analysis (See Chapter 5), it was felt that this had the potential to impact on experience and so a range was desirable. For example, there may be regional differences that impact on a GP's attitude towards research participation: Birmingham GPs, for example, may have different experience of research than their counterparts in Cornwall.

Table 15: Sampling criteria

Sampling Criteria
Recruitment group ➢ High (>60% eligible patients recruited) ➢ Low (<40% eligible patients recruited) ➢ Medium (40-60% eligible patients recruited) ➢ Small (<5 patients deemed eligible) Year of GMC Registration ➢ -1975 ➢ 1976-90 ➢ 1991- Practice Size (Number of GPs) ➢ 1-2 ➢ 3-8 ➢ > 8 Year of Study Training ➢ 2001-2002 ➢ 2003 ➢ 2004 Practice Location ➢ Hertfordshire ➢ Midlands ➢ Cheshire ➢ Gloucestershire ➢ Devon and Cornwall

7.2.2. Practice Selection and Invitation

All practices taking part in BAFTA were given a unique identity number and this number was used during practice selection to ensure that known practice names were not favoured. Practices were split into the four recruitment groups (See Table 14) and for each group, the identity numbers of all eligible practices were printed out, together with details of their characteristics per the sampling criteria. Practices were chosen from these lists in a manner that ensured that a range of criteria were represented. In order to make sure that GPs at the extreme end of each recruitment group were represented, GPs were invited in order of proportion of their eligible patients recruited, starting from the extreme of each group and moving inwards until the desired sample was achieved. (For example, GPs in the <40% group who recruited 0% of their eligible patients and GPs in the >60% group who recruited 100% of their eligible patients were invited for interview first). Due to the fact that the practice identity numbers were known to the interviewer, they were selected by one of the supervisors (Jonathan Mant); this ensured that well known GPs were not selected in preference to other less known practices.

Once selected, recruiting GPs within each practice were sent a letter describing the study; GPs were asked to return a reply by fax indicating whether or not they would be willing to participate in an interview. A secretary from BAFTA contacted the non-responders by telephone to determine whether they were willing to participate. When GPs refused, another practice with characteristics close to those who refused was chosen and approached.

Although this approach to practice selection was working successfully, it was a very time consuming process. It was considered vital that all interviews were carried out before the BAFTA results were published (See Section 7.2.1), so a more pragmatic approach to

recruitment was taken. All potentially eligible GPs were written to and the sampling was carried out from those GPs who had agreed to participate. Where specific characteristics were still required, GPs who had not responded were contacted by telephone to see if they would agree to be interviewed.

GP recruitment was planned to continue until theme saturation occurred. At the planning stage this number was unknown, so it was proposed that 20 interviews would be carried out. This number was selected in order to limit the chance of missing any important issues[158,159] GPs are a busy group of people, and can be difficult to engage in research[135,136] so it was anticipated that approximately 60 GPs would need to be approached in order to achieve this number. As there were 83 BAFTA GPs potentially eligible for interview, there was sufficient scope to be confident that this number could be reasonably achieved.

Based on a grounded theory approach, the original study design aimed to carry out data collection and analysis concurrently, so that data collection could continue until theme saturation had been achieved.[131] However, the time constraints imposed by the fast tracking of the BAFTA publication meant that this was not able to happen. A decision was taken to carry out as many interviews as possible within the time available, without the benefit of concurrent analysis; the risk with this approach is the possibility that saturation would not be achieved and that questions would remain about whether all possible opinions or experiences had been identified. However, within the time limits, it was possible to carry out the number of interviews that were initially estimated to be necessary, so it was hoped that saturation would still be achieved. It is acknowledged, however, that this was a risky approach that may have resulted in questions remaining about the experience of recruiting patients to BAFTA, and that this was potentially a shortcoming in this project.

7.3. Development of Interview Schedule

The development of the interview topic guide was based upon information gained from the existing literature, as discussed in chapter three, and on the findings of the earlier BAFTA analysis, as discussed in chapters five and six. The questions were worded to include the general topics thought to be important, but to allow the participants to express what was particularly important to them. It began with a general background, both to the GP and the practice, proceeded to explore issues specific to BAFTA, and concluded with an exploration of broader trial issues. GPs were given the opportunity to suggest whether any aspects of the trial could have been improved upon, and how this could have been achieved. Prompts were used, where appropriate, to delve more deeply into GPs' experiences. Although the topic guide was detailed, this was to ensure that all important subjects were covered, and served mainly as a reminder to the interviewer, rather than a rigid format for the interviewer to follow. The topic guide can be found in Appendix four.

7.4. Conducting the Semi-Structured Interviews

GPs who agreed to be interviewed were contacted by telephone to arrange a convenient time and location. They were offered the option of coming to the University where the researcher was based, or they could choose to have the interviewer visit them either at their practice, their home or an alternative location suitable for them. Although interviewing people in their homes can sometimes be difficult as there is the potential for distractions and interruptions, it was felt that offering total flexibility on time and location would minimise the number of GPs who would not take part due to logistic reasons.

At the start of each interview an explanation of the study was given, together with reassurances about confidentiality and anonymity. As it was likely that the GPs would be aware that the interviewer was also the BAFTA trial manager, emphasis was placed on the

fact that discussion of both positive and negative aspects of the trial would be welcomed. The GP and the researcher completed the consent form together. One copy was retained by the GP and one copy was retained for the research file. Provided consent had been obtained, the interview was tape recorded and then transcribed, either by the researcher or by an administrator as soon as possible after the interview. The first interview was transcribed immediately to allow assessment of how well the topic guide worked. The GPs name was not recorded with the transcript, and any other potential identifiers, such as the name of the practice or particular nurses, were concealed during transcription to preserve anonymity. The tapes and transcripts were stored in locked cupboards at the University; electronic copies were saved in password protected folders.

The interviews followed the previously mentioned topic guide, which can be found in Appendix Four. The topic guide began with background questions about both the GP and the practice and then asked for a description of the BAFTA study. Attitudes towards the trial question and drugs were discussed, followed by more detailed descriptions of their experience of taking part. GPs were given the opportunity to suggest whether any aspects of the trial could have been improved upon, and how this could have been achieved. The interview continued with questions about broader issues to do with trials and concluded with the opportunity for them to make any further comments. Respondents were asked about the trial in a general way, allowing them to focus on the areas that they considered important. Although the topic guide was used to ensure that all topics were covered during the interview, the interviewer allowed the GPs to talk about the issues important to them, in the order that they chose themselves, and used the topic guide as a memory aid rather than a strict order of questioning.

7.5 Interviewer Characteristics

The characteristics and orientation of the researcher are important and are considered part of the process of doing qualitative research: the behaviour and interactions of the researcher with the participants have the potential to lead to bias in the work.[160] For example, the professional background of the researcher has been shown to influence the interactions during interviews carried out as part of two qualitative studies looking at heart disease.[161] One interviewer was a GP, the other was a sociologist. The GP was open about her medical qualifications, whereas the sociologist introduced herself as a researcher and stressed that she was not medically qualified. Although there were some common interactions, many respondents spontaneously gave their often unfavourable views about medical professionals: this was not evident in in the interviews carried out by the GP.[161] In order to allow assessment of these potential biases, any relevant limitations or advantages of the researcher's ethinicity, gender, socioeconomic status or other relevant factors should be openly discussed.[162] There are two schools of thought with regard to how involved researchers should be with their subjects. One opinion states that if a researcher develops a close relationship with those being researched, the researcher may be blind to unpleasant facts, therefore introducing bias.[160] Alternatively it may be argued that if researchers develop close ties with their subjects, their ability to experience empathy will allow them to communicate at a more intimate level, thereby enhancing their ability to gain information that would otherwise not be obtained.[160]

In this study, the characteristics and orientation of the researcher may be particularly relevant, so it is important to consider the potential impact. One researcher conducted all interviews. She is female, aged 39 years and of white European appearance. The researcher is not medically trained but was very familiar with the BAFTA study, having worked on the study from the design phase, and having been the trial manager from 2003 until study conclusion.

The role that the interviewer had in BAFTA was not made explicit, either in the initial invitation or during interview. Despite this, it is likely that the majority of responders knew the interviewer and were aware of her role in the BAFTA study. It is possible that this relationship may have deterred GPs from giving honest opinions about negative aspects of the trial. In order to minimise this risk, care was taken during the interview to emphasise that there were no right or wrong answers to questions, and that their genuine opinion was sought. Negative comments were actively sought during analysis. However, a minority of GPs spontaneously raised the subject during interview, and explicitly stated that they would definitely be honest about negative opinions despite the fact that they were aware of the interviewer's association with the trial. It is therefore hoped that this prior professional relationship did not influence the content of the interviews.

It was also not explicitly stated to respondents that the interviewer was not medically qualified. It is not clear whether GPs were aware of this fact; they discussed medical facts in relation to BAFTA in some detail, and obviously assumed a prior knowledge on behalf of the researcher, so it is unlikely that this background influenced the discussions. However, the GPs were aware of the research experience of the interviewer, and a minority of GPs were explicit in their opinion that the interviewer had more knowledge about the research process than they themselves had. This may have had some influence on discussions about their understanding of technical terms associated with RCTs, as some GPs stated that they felt the interviewer would know the answer better than they would. However, they all went on to describe their understanding of the terms; again it is hoped that this knowledge had minimal impact on the content of the interview.

7.6. Respondent Validation

Respondent validation is a method of external validation which compares the investigator account with that of the inverviewees in order to establish 'the level of correspondence' between them[156] and is considered by some as the strongest check on the credibility of the research.[163] There are, however, limitations to their use as a validation test. For example, researcher accounts are likely to differ from individual accounts as the researcher account is designed for a wide audience. Therefore, it may be better to view respondent validation as a process of error reduction rather than a check on validity.[156]

Respondent validation was carried out in this project. This aimed to ensure that interviewee opinions were represented as they were intended and the researcher was not inadvertedly imposing her views on the data.[134] Each GP was sent a short one page summary of their interview transcript, together with a response sheet. They were asked to confirm whether or not the summary was a correct interpretation of their thoughts and to return the response sheet to the researcher by fax.

7.7 Data Analysis

There are a number of approaches that can be taken when carrying out analysis of qualitative data: one of the main considerations is whether the coding of the data is carried out inductively or deductively. A grounded theory approach is an example of inductive analysis: theories are allowed to 'emerge' from the data, through the process of analysis. This is a particularly useful technique to use when little is known about a subject, and it is not possible to predict what the findings are likely to be. The emphasis is placed on the development of theories as the final outcome of the analysis:[164] theory is defined as 'plausible (likely or probable) relationships between sets of categories which have emerged from data analysed….a statement about possible relationships among categories about a

phenomenon'.[165] An important feature of the grounded theory approach to analysis is the constant comparison technique: categories that emerge at one stage of the analysis are compared with those that emerged at a previous stage; this process continues until no new categories emerge and 'theoretical saturation' is achieved.

A different way to carry out qualitative data analysis is to utilise a deductive approach: when using deductive analysis, theories or categories have been decided in advance. This is an approach often used when conducting policy research, and The Framework Method of analysis, as devised by the National Centre for Social Research[166] is a good example. This approach allows the researcher to set categories at the start of the process; the data are then searched for examples that will correspond with them. However, the framework approach can share the same broad principles as the grounded theory approach, as it also enables inclusion of themes that may emerge from the data: the constant comparison technique can be utilised and the framework amended accordingly. Once the data has been categorised it is presented in the form of thematic charts and analysis of the data both within-case and between-cases can be carried out. With the framework approach, data analysis can stop at the level of description, or can continue in a similar vein to grounded theory approach until theories have been built and saturation achieved.[165]

For this particular project, a grounded theory approach would have been appropriate, as little was known about the subject area. Generation of theories about practitioner factors that impact on patient recruitment to trials that can be tested in further research would be useful. However, it was not possible to use grounded theory as the interviewer had substantial prior knowledge about BAFTA and had carried out an extensive review of the literature in this area. Therefore, Framework was used. However, the coding structure was developed

inductively from the data, as described in the previous paragraph. Coding and analysis were then carried out using Framework Software.[166] The remainder of this chapter will describe in more detail how the analysis was carried out, and will conclude with an explanation of how the results will be presented.

7.7.1 Development of the Coding Framework

Due to the time constraints described earlier (Section 7.2.2) all interviews had been completed prior to the start of analysis and it was therefore not possible to carry out concurrent analysis. Concurrent analysis would have been preferable, as it would have allowed adjustment of the interview schedule to explore themes in subsequent interviews that may have been emerging from the data during the early ones. In order to determine whether theoretical saturation had been achieved, transcripts from the first eight interviews were used to identify themes and provide the basis of the coding framework; constant comparison was then used for the remaining transcripts and the framework was adjusted where new categories or themes were continuing to emerge.

To identify themes in the data, one researcher read the first eight transcripts and noted all the subjects or keywords raised by the GPs on separate post-it notes. Generally, researchers note the points in the margins of the transcripts or on the analytical software being used at this phase of the process,[165] but it was decided that it would be easier to categorise topics if they were noted on individual sheets of paper; it did not matter, at this point, which interview the comments were taken from. This approach aided the thought processes of the researcher. Each point was then placed into groups and duplicate comments removed. Each group was given a category title, and these categories discussed with one of the supervisors (JM). The categories were then collated into three main themes and a basic coding framework was developed. To test the applicability and validity of the proposed thematic framework, one interview that had

not been used for the framework development was chosen at random and coded; following this, a number of changes were made to the coding structure and version two was produced. Two further researchers then coded this transcript. Following discussion and comparison of this coded interview, the themes were refined and version three of the coding framework was produced. All interviews were then coded using this final version of the framework. A table depicting the coding structure can be found in Appendix Five.

7.7.2 Carrying out the Analysis

Once the framework had been developed, all transcripts were imported into the software and coded. Inter-rater reliability was carried out to ensure rigorous data analysis:[134] the first eight interview transcripts were coded by two researchers and their coding was then compared to look for consistency and variation. Any disagreement was discussed and agreement reached. The remaining interviews were coded by one researcher. Following the coding, thematic charts were produced.

Following production of the charts, the next stage in the analysis involved between-case comparison: this aimed to identify the variety of experience between interviewees, for each theme. Between-case comparison also aimed to explore whether typologies exists, looking for common explanations or experiences between GPs. Typologies, as described by Ritchie and Lewis are:

> *Specific forms of classification that help to describe and explain the segmentation of the social world or the way that phenomena can be characterised or differentiated. They may apply to groups of people within the population or to sets of phenomena, like beliefs, circumstances or behaviours*[134 *(p 214)*]

Essentially they are patterns within the data, for example, GPs who recruited successfully may have a similar experience of research, but this experience may differ from the experiences of GPs who recruited less well. Therefore, for this study, typologies attempted to identify any groups within the sample who had similarities in their attitudes towards or experience of research, and to determine whether there were different typologies in one recruitment group than there were in others.

To identify typologies, the data was grouped together by different interviewee characteristics, and frequencies of different experiences were sought. Patterns within the data were then examined to illuminate any factors that might predict outcomes, such as demographic characteristics that may predict the way participation in research is experienced. Once these factors had been examined, within-case analysis was carried out to consider patterns within the data by investigating links between themes. For example, within-case analysis may demonstrate that GPs who describe a negative experience of participation also have a low tolerance for the risk posed to their patients by exposure to trial drugs. Utilising these techniques applied a structured approach to data extraction, grouping and analysis.

7.8 Presentation of Results

There are two schools of thought in presentation of qualitative results: to include numbers (of individuals who raise each point under discussion), or to exclude numbers. The results are presented, in this thesis, to represent frequency of views in a general way rather than presenting numbers of interviewees for each theme or concept. This choice was made for two reasons: firstly it is suggested that inclusion of numbers can detract from the reading style and secondly, there is no indication as to how these numbers should be interpreted:[134] because the sampling strategy does not aim to identify a statistically representative population it may be misleading to express relative frequencies of responses.[167] Use of more general terms can

indicate dominance of views in a way that would be more difficult to interpret if using numbers,[134] and is a style that is represented in a variety of journals.[168]

Chapter 8: Interview Results

This chapter reports the results of the final stage of this project, the semi-structured interviews. It will begin by giving details of uptake rates and an overview of the interviews. Details about the demographic characteristics of respondents are given, explaining to what extent the aims of the purposive sampling were met. The chapter will then put forward the themes that emerged from the interviews, presenting quotations to illustrate these themes.

8.1 Overview of the Interviews

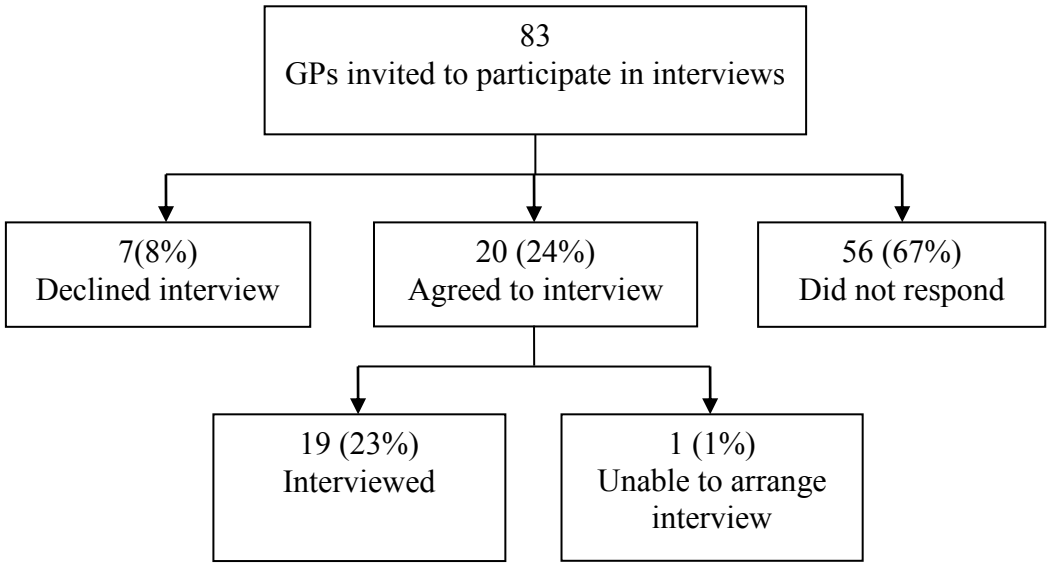
Interviews were conducted up to 18 months post BAFTA patient recruitment and approximately six months post patient follow up. All were conducted before the trial results were available. The interviews varied in length (between 30 and 90 minutes) depending upon how much time was available to the GP for the interview. Fifteen of the interviews were carried out at the GPs' surgeries; three within their homes; and one was carried out at the University. The three carried out within the GP's home were longer (approximately 90 minutes); two contained interruptions where the interview had to be paused for a time (one was interrupted by children entering the room, the other by a telephone call). The shortest interview (approximately 30 minutes) was where the GP was late because they had been delayed while carrying out home visits and were unable to extend the end time as they were due to start afternoon surgery. In two interviews carried out at surgeries, there were also interruptions that caused the interview to be paused (in one, the GP had to interrupt the interview to attend a short meeting; in the second, the interview had to be moved to a different room). The topic guide was used throughout (See Appendix Four).

8.2 Uptake Rates

As described in section 7.2.2, two approaches to inviting GPs were taken: both produced very different results in terms of the numbers responding to the invitation and agreeing to interview. Figure 13 gives the overall uptake rates for the study.

Whilst inviting GPs to participate during phase two of recruitment, care was taken to ensure that the sampling requirements were being fulfilled (discussed in detail below). Nineteen GPs were interviewed, but only 17 were included in the analysis (two interviews failed to record). One GP did not consent to the interview being recorded so notes were taken during the interview; the notes were subsequently included in the analysis, although no direct quotes were taken from this interview.

Figure 12: Recruitment Overview of Interviewees



8.3 Participant Characteristics

As described in section 7.2.1, purposive sampling was attempted to gain variation in interviewees (in age, proportion of eligible patients recruited, practice size, year of training), and therefore variation in experience. Table 15 shows the characteristics of the participants.

Table 16: Characteristics of the Participants

Interview No.	Gender	Year of GMC Registration	Practice Size	Practice List Size	Region	Recruitment group	Year of Training
1	F	1970	5	8053	Herts	>60%	2003
2	F	1977	6	12600	Midland	40-60%	2001
3	F	1980	4	7696	Cheshire	40-60%	2001
4	M	1985	4	6500	Glos	<40%	2003
5	M	1979	3	4439	Glos	40-60%	2003
6	M	1981	4	4237	Midland	<40%	2002
7	M	1996	6	12133	Devon	<5	2004
8	M	1969	7	8269	Devon	>60%	2004
9	M	1979	6	4744	Midland	>60%	2001
10	M	1993	16	14028	Herts	40-60%	2003
11	M	1984	5	8880	Herts	>60%	2003
12	F	1982	5	9400	Herts	40-60%	2003
13	M	1989	5	8900	Cornwall	>60%	2004
14	F	1988	10	18000	Herts	<5	2003
15	M	1985	3	4571	Midland	40-60%	2001
16	F	1996	4	6878	Glos	<5	2003
17	M	1991	5	5850	Midland	<5	2001

Having looked at the individual characteristics of participants, it is important to establish whether the sampling aims have been fulfilled, especially given the challenges faced during sampling. Table 16 (page 150) contains a summary of the characteristics of participants. As can be seen from the first four sections, all of the sampling aims were fulfilled, with the exception of inclusion of a GP from a practice with one-two partners. Although one GP from this category was interviewed, this was unfortunately one of the failed interviews. The remaining sections of the table demonstrate that there was representation from all of the other potentially important factors.

Table 17: Summary of Participants' Characteristics

Recruitment Group	
High (>60%)	√√√√√√
Low (<40%)	√√
Medium (40-60%)	√√√√√
Small (<5 patients deemed eligible)	√√√
Year of GMC Registration	
-1975	√√
1976-80	√√√√
1981-85	√√√√√
1986-90	√√
1991+	√√√
Practice size (No GPs)	
1-2	
3-4	√√√√√√
5-6	√√√√√√√
7-8	√
>8	√√
Year of Training	
2001	√√√√
2002	√
2003	√√√√√√√√
2004	√√√
IMD Quartile	
1 (Least)	√√√√√
2	√√√√√
3	√√√
4	√√√
Gender	
Male	√√√√√√√√√
Female	√√√√√√
Region	
Hertfordshire	√√√√√
Gloucestershire	√√√
Midlands	√√√√
Devon/Cornwall	√√√
Cheshire	√

The lack of very small practices is a significant omission from the sample, especially when considering the significance of practice size in earlier analysis (See Chapter Five). The potential impact of this will be discussed in section 9.1.

8.4 Responder Validation

Of the sixteen GPs who were sent a summary of their interview transcripts, nine GPs returned a response. All nine indicated that they agreed with the summary and none expressed any concerns or objections to this initial interpretation of their comments.

8.5 Interview Themes

The interviews aimed to understand the GPs' experiences of recruiting their patients to an RCT, uncovering their reasons for deciding to take part, identifying how they carried it out and understanding how they felt about the process. Suggestions for improvements were also sought. The order in which topics emerged was influenced by the topic guide, but not exclusively driven by it; some GPs, for example, would discuss the responsibility they feel for their patients with regard to involving them in trials when talking about their reasons for deciding to take part.

Three main themes emerged from the interviews: risk and responsibility; doctor/patient interaction; and GP motivation, experience and understanding (See Table 17, page 152). Each theme will be presented individually, broken down into sub-themes and supported by verbatim quotes from the interviews. Sub-themes as presented will not necessarily be identical to those found in the coding framework (See Appendix Five): some sub-themes are intrinsically linked and will be presented together for ease of explanation and understanding. The quotations were selected on the grounds of representativeness.

Table 18: Emergent Themes

Theme	Description
Risk and Responsibility ➢ Risks of BAFTA ➢ Risks of enrolling patients into trials ➢ Ethics of trials ➢ GP Responsibility ➢ Changes in attitudes to BAFTA	How GPs felt about the risk associated with trials, and the uncertainty around the study treatments, to include reasons for participation, the ethics of RCTs and the responsibility they feel towards their patients.
Doctor/Patient Interaction ➢ Explanation of the trial ➢ Doctor/Patient relationship ➢ Patient experience & understanding ➢ Clinical autonomy	How the GP explains the trial to patients, to include discussion of trial drugs, randomisation and uncertainty, how GPs think their patients feel about trial participation and their need for information, and thoughts about clinical autonomy.
GP Motivation, Experience & Understanding ➢ Motivations for taking part ➢ Overall experience ➢ Interaction with the BAFTA study team ➢ BAFTA Training ➢ Practicalities ➢ Understanding ➢ Suggestions for improvement	To include understanding of BAFTA and trial principles in general, issues affecting recruitment (including practical considerations), relationship with the study team, benefits for the practice and suggestions for future improvements.

8.5.1 Risk

The concept of risk runs through many of the decisions that GPs took about recruiting patients to BAFTA, from the initial decision to participate to the choice of patients they considered appropriate for inclusion. This section will start by presenting GPs' discussions of the risks associated with involvement both in BAFTA and with trials in general, and will continue with their perception about the ethics of trials and the responsibility they feel for their patients. The section will conclude with changes in GP attitudes over the course of the trial.

8.5.1.1 The Risks of BAFTA

When asked to describe the study, a significant majority gave a correct description of the study as being a trial of aspirin versus warfarin for stroke prevention in older people with AF.

"the purpose of the trial I understood was to, to decide whether aspirin or warfarin was the best treatment for people in atrial fibrillation to prevent er strokes and other complications, and to minimise the erm side effects of those drugs themselves in causing problems"

Interview 5 (Male; medium recruitment group)

All interviewed GPs discussed their views about the risks associated with the drugs in question. Aspirin and warfarin were regularly used in practice to manage the stroke risk of patients with AF, so they were both drugs that GPs were very familiar with. Most GPs acknowledged that warfarin was the superior treatment for younger patients, but some described it as a potentially dangerous drug for older people, and they were often concerned about prescribing it for them.

"at the time when we were thinking of going into the trial, you know, certainly some of the GPs were very unkeen on prescribing warfarin and very keen to look for excuses not to"

Interview 3 (Female; medium recruitment group)

"obviously we were all worried about polishing people off with warfarin"

Interview 5 (Male; medium recruitment group)

One GP described the risks to their patients posed by the study drugs in a slightly different way. Although this GP acknowledged the risks associated with warfarin, he felt that it had

been shown to be the most effective treatment and he described how he considered the risk of exposing his patients to aspirin.

> *"the gut feeling was they hadn't had a, a very much inferior treatment for it now so we felt quite safe to expose them to the aspirin"*
>
> Interview 13 (Male; high recruitment group)

Although the dangers posed by warfarin were often discussed, it did not seem to deter GPs from participating in the trial; the majority seemed to balance their concerns with a variety of factors that offset the perceived risks associated with these drugs, and thus justified the potential exposure of their patients to the trial. For example, most GPs considered the trial question important, describing how AF is an increasingly common problem that is often seen in general practice. Its importance was felt to be increasing because responsibility for the ongoing care of people with AF was now falling more on general practice than it had previously.

> *"atrial fibrillation and warfarinisation, it's quite an important issue because we have to make these sort of decisions quite regularly"*
>
> Interview 2 (Female; medium recruitment group)

> *"I think atrial fibrillation is becoming much more the domain of primary care now as opposed to secondary care, there has been a real shift in that"*
>
> Interview 16 (Female; small recruitment group)

BAFTA was further described by many GPs as being important because of its clinical relevance, partly because of the increasing number of patients diagnosed with AF and the shift to primary care of its management, but also because of the ongoing uncertainty surrounding the best way to manage a patient's stroke risk. Most were aware that they were regularly making decisions about use of warfarin without an adequate evidence base to support it.

"there wasn't sort of definite evidence as to what we should be doing"

Interview 14 (Female; small recruitment group)

"you never really do know what you should be putting people on"

Interview 16 (Female; small recruitment group)

The clinical relevance was further highlighted by the implications for people, especially older people, of taking warfarin. Warfarin involves regular monitoring, care needs to be taken that it is taken correctly and ongoing consideration of changing risk factors needs to be taken into account. GPs face these dilemmas each time they encounter an older patient with AF and they were keen to ensure that they were making decisions that were in the best interest of their patients.

"there is no doubt that putting 80 year olds on warfarin has a lot of implications, if only because it's a hassle, they have to go and have their bloods checked, erm, and I don't think I would want to do it without being fairly sure that I wasn't doing them any harm"

Interview 12 (Female; medium recruitment group)

"always posed a dilemma when you see an elderly patient with atrial fibrillation whether to warfarinise them……you're never quite sure about the risk/benefit ratio really"

Interview 10 (Male; medium recruitment group)

A minority of other GPs described the risks to patients of sub-optimal management of the risks associated with their AF, and felt that BAFTA was an important study because of the 'major' nature of having a stroke.

"the proportion of those [older people with AF] *are having strokes which is a devastating thing"*

Interview 5 (Male; medium recruitment group)

The relevance and importance of the trial question convinced over half of the GPs that practice participation in BAFTA would be of benefit to their patients, both existing patients with AF and those who develop it in the future, and so felt that justified the potential risks of taking part.

"we thought it would really be serving our patients' needs if we could come up with clear cut answers… it would make a difference to patient care"

Interview 2 (Female; medium recruitment group)

Having talked about the risks associated with warfarin, nearly all GPs went on to describe how they felt that BAFTA was a relatively safe study. Although warfarin was considered potentially dangerous, it was felt that enough was known about the drug to be able to assess

that risk. However, almost all GPs would not like to take part in drug company led research as this is often testing experimental drugs.

> *"After that recent hmm drug problem in Oxford everyone worries…as a practice we wouldn't be involved in any drug company led research. We were quite happy with academic led"*
>
> Interview 2 (Female; medium recruitment group)

The majority of GPs felt confident that BAFTA was well controlled, with independent bodies who monitor progress and would stop the trial if something was going wrong.

> *"Built into the trial that is something is beginning to go wrong, someone is looking into it and picking it up on a relatively early basis"*
>
> Interview 6 (Male; low recruitment group)

A few also felt confident in the trial because it was being run by an academic department within a University. A small minority of GPs described how they felt supported by the University and this contributed to a feeling of safety.

> *"with your study I felt very supported every time I needed to ask a question"*
>
> Interview 16 (Female; small recruitment group)

> *"erm, you know, we felt safe"*
>
> Interview 11 (Male; high recruitment group)

8.5.1.2 The Risks of Enrolling Patients into Trials

Even when GPs felt comfortable with the level of risk posed by a particular trial, about half still had concerns about the potential impact of enrolling their patients. A few GPs were worried about randomising their patients to different treatments; if anything should happen to one of their patients during a trial they would find that difficult to live with.

> *"if something dire happens to a patient while they're in the trial, that is a bit difficult to square"*
>
> Interview 6 (Male; low recruitment group)

One GP explained that, while he understood that trials would be stopped if they were doing too much harm, people still need to be hurt before it gets to that point, and if it was his patients that were hurt then he would be upset about it.

> *"but you have to hurt a few people on the way to get that data and if it's my patients then I would feel upset about it"*
>
> Interview 11 (Male; high recruitment group)

Other GPs had a more pragmatic approach to their concerns around the risks to their patients of trial participation. They felt that if they were happy with the trial concept, then their role is to portray the risks to their patients appropriately, and ultimately it is the patient's decision whether or not to take part.

"I think it's having a clear understanding…really satisfying yourself that you've explained that sufficiently to patients, erm, for them to be able to make the decision, erm, so no I don't have an issue with that"

Interview 10 (Male; medium recruitment group)

One GP, however, spoke about his concerns about recruiting his patients to trials in a more general way. Although acknowledging that there are differing levels of risk associated with different studies, when asked how he felt generally about involving patients in trials, he stated that "I am very frightened about it" (Interview 4). On the other end of the spectrum, another GP described how he felt that although patients look at risk differently from doctors, the information provided by trials is necessary, so it is important to enrol patients into studies.

"we know the patients look at the risks differently from the risks that doctors do, but we badly need more information in the older population"

Interview 9 (Male; high recruitment group)

A minority of GPs discussed how the acceptable level of risk depends on the ability of patients to understand and accept the risks involved; for studies like BAFTA, involving known drugs, it would still be acceptable to include patients who would have difficulty understanding the concepts of unquantifiable risks associated with testing newer drugs.

"these were a fairly standard treatment, so you weren't exactly exposing them to a great deal of risk, hmm, and an unquantifiable risk either… if you are using a really cutting edge new treatment…. Then

that's different. I think people have got to know and understand a lot more then"

Interview 8 (Male; high recruitment group)

One GP explained how he hoped not to do harm by involving patients in trials, but felt that if you worried about it too much it would influence the selection of patients to be included, and this would influence the findings.

"if everybody quite cautious only submits the best five patients… then you have to possibly question the results of that particular study"

Interview 13 (Male; high recruitment group)

8.5.1.3 The Ethics of Trials

During interviews GPs were asked about their thoughts on the general ethics of trials, including their views on randomisation. Some GPs also discussed the role of ethics committees as part of this subject area. These will be presented in this section in turn.

Ethics of Trials

During interview GPs were asked to talk about how they felt about the randomisation of patients. All GPs discussed it in the context of the ethics of a trial, and said that they understood the need for randomisation and had no problems with it as a concept.

"I don't have a problem with that because I think if you want to find out things you have got to do this"

Interview 15 (Male; medium recruitment group)

Having agreed with the concept, all GPs went on to qualify their belief and discussed a variety of conditions that need to be met if randomisation is to be ethical. Almost all GPs said that it depends very much on what patients are being randomised to. There needs to be no clear disadvantage to patients in one of the treatment arms, and this makes trials with a placebo arm more difficult.

> *"there's no other comparison with other treatment options you know with placebo and a treatment, I think that is quite difficult"*
>
> Interview 2 (Female; medium recruitment group)

A significant majority of GPs said that it was ethical only if there was no clear cut evidence for one of the treatments under investigation. This was also true at the individual patient level. Most GPs felt that they needed to not only be generally unsure as to the best treatment for a condition, but for each individual patient they also needed to be unsure as to the best treatment option.

> *"if you genuinely don't know the answer to the question and you genuinely don't know what is best for the patient, then I've no ethical issues with the randomisation"*
>
> Interview 3 (Female; medium recruitment group)

Most GPs also said that patients need to be fully informed about the trial, aware of the randomisation element, and be happy to be involved for randomisation to be ethical. A minority also said that they felt it was important for the ethics of a trial that patients were aware that they could withdraw at any time.

"Patients have to know whether there is a likelihood they'll get a placebo or that they are taking part in a trial. And I think it is equally important to let patients know that they can drop out"

Interview 16 (Female; small recruitment group)

A minority of GPs felt that to randomise was actually more ethical than to not randomise. Non randomised trials would allow recruiters to select patients they liked to go on the drug they liked and this would call the trial results into question. One GP felt that it was more ethical to randomise than to continue using the wrong treatment. Furthermore, another GP felt that clinicians are often too influenced by drugs representatives, and that this practice is more ethically questionable than the randomisation of patients.

"otherwise you have like an unethical way… if you're trying to push everyone onto that arm and don't randomise it and all the people you don't like you give the other stuff, then, that's when I think you have problems"

Interview 13 (Male; high recruitment group)

"it seems ethically much better to try and find out the best treatment rather than just carry on randomly using the wrong treatment"

Interview 8 (Male; high recruitment group)

"we as doctors are historically notorious for taking too much notice of… drug reps and that to me seems much more ethically debatable than putting people into trials"

Interview 12 (Female; medium recruitment group)

When asked about how they felt generally about involving patients in trials, almost all GPs raised concerns about the ethics of involving patients in drug company funded trials, as they felt that these are ethically more questionable than NHS funded or academic type trials. Many questioned the motivation, feeling that the aim of these trials was to prove that their drug was superior, rather than to genuinely discover the most effective treatment. They felt that the question was often couched in such a way as to provide an inherent bias towards their drug of choice.

> *"drug sponsored trials, they want to prove their drug is best. And they will compare it with ones that they know are not as good erm, and they will selectively erm look at things, they may use sub-groups or different forms of statistical analysis or whatever to prove their drug is right"*
>
> Interview 3 (Female; medium recruitment group)

About half of the GPs felt that drug companies often failed to publish the results of trials that were not favourable to their drug, and that pressure was put on them to use their drug at the end of trials. Some of these GPs were put off participating for those reasons, while others felt that they may still get involved if there was an independent clinician involved in the trial management.

> *"we are pretty anti drug company erm, I have a lot of qualms… all the drug company research that hasn't been published for instance… you probably know why, and erm often there's a lot of pressure to use*

their drug afterwards and I don't like that at all… I think you'd want it done by somebody impartial really"

Interview 5 (Male; medium recruitment group)

A minority of GPs felt that a direct link between payment and recruitment made a trial unethical. Putting pressure on practices to recruit a specified number of patients may encourage them to enrol unsuitable people, and direct payment for recruited patients was felt to encourage this.

"that a minimum number and a certain payment is triggered, well I think that would then get to the unethical side… that aspect I would be very uncomfortable with then"

Interview 13 (Male; high recruitment group)

Ethics committees

Many GPs felt that ethics committees played a central role in their judgement about the ethics of an individual trial, contributed to their decision to participate, and felt that ethical committee approval would ensure that patients were not asked to do anything that involved too much risk to themselves.

"to get a trial approved now it has to go through fairly extensive review from medical ethics or what not. So it's very unlikely that anything particularly risky is going to be asked of a patient"

Interview 15 (Male; medium recruitment group)

However, one GP pointed out that delays caused by the ethics approvals process can cause problems for practices wishing to participate, and urged researchers to act to minimise this delay.

> *"it was held up at the ethics committee wasn't it? And that's very unfortunate, that really really is unfortunate… it is a major problem because… people would very rapidly lose interest in something like that"*
>
> Interview 1 (Female; high recruitment group)

8.5.1.4 GP Responsibility

GPs were asked about how responsible they would feel if harm was done to one of their patients as part of a trial that they had enrolled them onto, and it transpired that the patient had been taking the inferior treatment. Almost all GPs said that they hope not to do harm to the patient, but they would not feel responsible for the inferior treatment because they did not know that was the case when the patient was enrolled. One GP felt that despite this, patients would hold him responsible.

> *"You did it with the best information that you had at the time, no I'm completely definite about that, that's not my responsibility"*
>
> Interview 9 (Male; high recruitment group)

> *"I know in my heart of hearts that I am not responsible but I'm sure the patients might blame"*
>
> Interview 4 (Male; low recruitment group)

The majority of GPs felt that the trial would not change the responsibility they feel for patients, because it is the prescribing or changing of drugs that they feel responsible for, rather than inclusion in the trial.

> *"I don't think the difference is the trial, I think the difference between if someone suffers you know, as a consequence of their illness, then that's not so bad, but when it's a consequence of your intervention then that's when it feels uncomfortable"*
>
> Interview 7 (Male; small recruitment group)

A few GPs felt that inclusion in the trial actually took some of that responsibility away from them, and felt that was why it was so important to be happy with the trial concept from the outset.

> *"I felt that this other responsibility had been lifted really, for putting people on warfarin, that it wasn't really so much my responsibility, whereas I was sticking my neck out by putting them on warfarin without any hard and fast evidence"*
>
> Interview 5 (Male; medium recruitment group)

> *"I would feel equally bad, er probably feel worse because it's truly my choice without any prompting from a well designed trial, so I would probably feel less responsible… I would dread it more making some mistake in other aspects which is genuine"*
>
> Interview 13 (Male; high recruitment group)

Responsibility was also mitigated by the fact that patients are also involved in the decision to participate. A minority of GPs said that they also bear some of the responsibility, so long as the risks had been explained to them adequately.

> *"you do feel a certain responsibility …. Because if it wasn't for you they wouldn't be in the trial… but equally they are an adult, they can make their own decisions"*
>
> Interview 16 (Female; small recruitment group)

A small number of GPs also discussed the responsibility they have towards carrying out research. One GP felt that taking part in a trial meant that you have responsibility, not only to the patient, but to the trial too, and this dual responsibility needed to be balanced.

> *"if you're involved in a trial you've got a duty of care to the patient, but you've also got a second obligation which is to the trial, and its balancing the erm, that out"*
>
> Interview 10 (Male; medium recruitment group)

Others described how they felt that GPs should be responsible for carrying out research, because general practice was a speciality in itself and so should be responsible for providing its own evidence base. Furthermore, the large numbers of patients available in primary care ensured that it is the optimum place for carrying out large studies.

"we have to be prepared to prove in primary care and do the research… research should be inherent in medical training and people shouldn't be allowed to stop"

Interview 12 (Female; medium recruitment group)

"you have the numbers…. General practice should be used for this large numbers type studies"

Interview 2 (Female; medium recruitment group)

8.5.1.5 Changes in Attitudes towards BAFTA

BAFTA recruitment was carried out over a four year period. It is possible that changes in GP attitudes towards the study question or the drugs involved took place over this time; maybe new guidelines, or an increased awareness of existing guidelines would change clinicians' perspectives and this may impact on their level of patient recruitment.

The majority of GPs said that they had changed their opinion over the course of the trial. Almost all of them described a different attitude towards prescribing warfarin for this patient population. Many talked about a general increase in the acceptability of warfarin for use in older people over the course of the trial, even pressure on GPs to prescribe it. At the start of the trial, many were nervous about prescribing warfarin:

"at the time we started doing it I think the jury was sort of really rather out on whether warfarin should be prescribed. I think things have shifted….when we were thinking of going into the trial… some of the GPs were very unkeen on prescribing warfarin and very keen to

look for excuses not to, where as now, you're sort of negligent almost if you don't"

Interview 3 (Female; medium recruitment group)

"I do know that the sort of, the pressure upon us to give warfarin in anybody in AF is across the age range, seems to be definite"

Interview 12 (Female; medium recruitment group)

When asked why they thought that there had been this shift in attitude, a few GPs alluded to trials that had been published during the BAFTA recruitment period that suggested this was a good thing, or mentioned guidelines that advocated warfarin use. However, they were not sure that this attitude shift was evidence based.

"my impression is that clinically it's not evidence based, since the start of BAFTA we've moved that way and now we use warfarin clinically much more widely, but I don't know if that's right"

Interview 6 (Male; low recruitment group)

A minority of GPs felt that their attitude towards prescribing warfarin for older people had changed as a direct result of their participation in BAFTA. They realised that giving warfarin to the over 75s was not necessarily too different than giving it to younger people.

"I realised probably by giving it to the elderly population are not too dis-similar to giving it to the under 75s….I think my opinion changed because the people who were randomised to warfarin seemed to cope with it really very well…. I was pleasantly, you know, surprised really

at the ease with which people did adapt to these sorts of regimes so it did change some of my view points about it"

Interview 16 (Female; small recruitment group)

"I sort of noticed, it's not the age really, that matters its hmmm, ... but how the person is functioning ... the chronological age really that seems to be that important"

Interview 2 (Female; medium recruitment group)

About half of the GPs felt that the trial had given them a better understanding of the issues around older patients with AF and managing their stroke risk. Additionally, having more patients on warfarin as a consequence of the trial improved their experience of dealing with it, thus giving them a different perspective on the risks.

"I kind of feel I have changed and I would be a lot more adventurous about the slightly older age group because I feel my understanding has improved"

Interview 2 (Female; medium recruitment group)

8.5.2 Doctor/Patient Interaction

The second theme to be addressed is doctor/patient interaction. Discussions that GPs have with patients about research may be different in content than standard consultations, and GP concerns about raising the subject may impact on these discussions. This section will present GPs thoughts about this, and will start with a description of how GPs explained the trial to patients, including any concerns that were raised about discussion of trial concepts. It will continue with the impact involvement in trials may have on the doctor-patient relationship,

including GP thoughts about clinical autonomy when participating in trials, and will conclude with GP thoughts about how patients felt about trials.

8.5.2.1 Explanation of Trials to Patients

GPs used different ways to explain the trial to patients, although most used the patient information sheet as a starting point. Some GPs tried to keep it as close to a usual consultation as possible by establishing what patients already understood and tailor the subsequent conversation accordingly.

> *"you quickly then establish what they understand and you can tailor to it"*
>
> Interview 9 (Male; high recruitment group)

Most GPs explained AF to their patients, and the risks associated with it. They continued, discussing the treatment options and explaining the pros and cons of each option. Some GPs kept this explanation very simple, explaining that aspirin thins the blood, and warfarin is a stronger version of it, while others explained in more detail.

> *"aspirin most people know thins the blood… warfarin is a stronger version of that… it would have been quite simple"*
>
> Interview 4 (Male; low recruitment group)

> *"we know aspirin reduces that risk by about a third, we know that warfarin decreases it by about two thirds"*
>
> Interview 9 (Male; high recruitment group)

At this point in the discussion, GPs would discuss the uncertainty around the treatment options to patients. All GPs explained the risks and benefits, but a minority felt that it was difficult to explain the comparison, and were not sure how well this had been done.

> *"it's difficult because it is a slightly technical comparison and to put it in terms that people can understand and I wonder if retrospectively it was… the concept or if it was the way I described it"*
>
> Interview 14 (Female; small recruitment group)

Most GPs described treatment uncertainty with a mix of general scientific uncertainty, and personal uncertainty. Most used the phrase 'we don't know' (i.e. the scientific community) but were happy to admit to their patients that they did not know the answer either. One GP described how he did not like to leave patients with uncertainty and so would focus on the facts that are known and minimise the impact of what is not known.

> *"I'd say to patients we know an awful lot…we don't know enough about this… I don't use the word uncertainty because I think it sends them away with a feeling of unease… it's different words but I hope it sends them away without the burden of uncertainty"*
>
> Interview 9 (Male; high recruitment group)

For patients happy with the concept so far GPs would continue, describing randomisation. Most would use a simple analogy, for example, like the flip of a coin. A minority said that a computer decided, but other GPs felt that patients would not like that and so used alternative explanations. Others 'passed the buck (and said that) the lady in Birmingham decides' (Interview 7).

"the best way to do that really, on the toss of a coin and then compare the people on one drug with the people who are on the other drug"

Interview 10 (Male; medium recruitment group)

"I wouldn't put a computer in charge of a basic clinical decision for a patient, they wouldn't like that"

Interview 1 (Female; high recruitment group)

Almost all GPs did not explain the need for randomisation, as they did not see a reason to do so: no patients asked them for further explanation. Those that did describe the need aimed to keep it as straightforward as possible.

"the reason for that is we need to make sure that we don't, you know, select certain patients… but I didn't go into the nitty gritty of the randomisation and why. Nobody asked"

Interview 10 (Male; medium recruitment group)

About half of the GPs described difficulties they encountered when explaining BAFTA to patients. As mentioned earlier, some found it difficult to explain the comparison between the two treatments. Others felt that uncertainty was much more difficult to explain to patients already taking one of the treatments because they may need to change.

"Some of them you see were already on treatment anyway, so they have to be told that there is a possibility you might be randomised to the alternative"

Interview 11 (Male; high recruitment group)

8.5.2.2 Doctor/Patient Relationship

The majority of GPs felt that involvement in trials did impact on the doctor/patient relationship. Two GPs said that the relationship did not change, and felt that if you had faith in the trial it should not influence it in any way.

> *"it would only do it if you didn't believe in the trial surely… you're not co-ercing them to do anything, you should have a belief in what you are doing is worthwhile and therefore no, I don't think it does"*
>
> Interview 14 (Female; small recruitment group)

GPs described different influences that involvement in a trial has on the doctor/patient relationship. Most felt that the changes were positive, and helped strengthen the relationship.

> *"they might be a little bit more familiar with you, which is alright"*
>
> Interview 9 (Male; high recruitment group)

> *"the few that erm went on to warfarin got a lot more attention, and I got to know them a lot better…I would have thought that was advantageous rather than disadvantageous to the patient"*
>
> Interview 5 (Male; medium recruitment group)

A minority of GPs had mixed feelings about whether the impact was positive or negative, and felt that depending on the situation, it could go either way. One GP felt that if patients started to expect more from you as a result of participation in a trial, then that could be a problem, but did not encounter that problem when taking part in BAFTA.

"I don't know if it is a good thing or a bad thing, but you kind of develop a relationship with people you spend a bit longer with…. The downside thing is because they very much feel that they are doing you a favour"

Interview 16 (Female; small recruitment group)

Another GP felt that it would be a good thing if it enabled patients to discuss issues with you that they would otherwise not bring up.

"It would be a bad thing if it started to influence the way they fed back to you if they were unhappy… equally you could argue it, if you had a better relationship maybe they could say things so it's really difficult"

Interview 11 (Male; high recruitment group)

8.5.2.3 Patient Experience and Understanding

GPs were asked their opinion about what they thought about how the patient experienced the trial. Most felt that the patients enjoyed the experience of participating, were pleased about the extra attention they got as part of the trial, and enjoyed the almost social aspect of the follow up appointments. A minority of GPs felt that their patients were altruistic and enjoyed giving something back.

"It became quite a social event"

Interview 6 (Male; low recruitment group)

"some people just enjoyed having some medical attention every few months which they didn't think they qualified for"

Interview 5 (Male; medium recruitment group)

Overall, most patients were felt to understand the trial and what they had agreed to participate in. A small minority of GPs questioned how far the patients understood the process or the reasons for randomisation, though most felt that patients understood that neither they nor the GP would choose the treatment they were assigned to.

> *"he wouldn't have understood the principal of randomisation presumably, I don't know. But he understood he was given a choice to be in the trial or not in the trial, and if he was in the trial he had to agree to what the Birmingham lady said"*
>
> Interview 5 (Male; medium recruitment group)

> *"probably thought to some extent that you'd decided this was the best treatment for them"*
>
> Interview 3 (Female; medium recruitment group)

There were mixed opinions on the extent to which patients understood the risks that had been explained to them. About half of the GPs felt that patients had a good understanding of the risks of the trial drugs, and of stroke, while others were not sure how well this was understood.

> *"they appreciated that warfarin overall would reduce their risk of stroke"*
>
> Interview 7 (Male; small recruitment group)

"you can explain it but even when you have explained it the patient may not appreciate the full implications"

Interview 15 (Male; medium recruitment group)

When asked what information patients wanted to be given before they made the decision whether or not to enrol, the majority said that they felt it was important that patients understand that they can change their mind and opt out at any point.

"as long as there's exit criteria that the patient can decide, I think that is important actually"

Interview 2 (Female; medium recruitment group)

8.5.2.4 Clinical Autonomy

GPs were asked about clinical autonomy and whether they had any thoughts about how trial involvement may impact on that. Most said that they had no concerns about the impact of BAFTA on autonomy as they retained the right to change or stop treatment, or to withdraw patients from the trial.

"I didn't have a problem at all.....it wasn't an instruction I was following regardless"

Interview 7 (Male; small recruitment group)

Over half of the GPs felt that autonomy was not an issue because uncertainty was not a good place to be autonomous from.

"If you don't know the erm, what's right thing to do genuinely, then I, I can't see that's a very good place to be autonomous from"

Interview 5 (Male; medium recruitment group)

"It's not a problem for me with that 'cause we don't know what the best thing to do is"

Interview 11 (Male; high recruitment group)

One GP felt that autonomy was not affected by trial involvement unless the trial specified what drug the patient was to remain on after trial completion; they would not choose to be involved in research that did not allow them that freedom of choice.

"They would put them on a specific treatment and then we would have to continue afterwards, and we said no we are not going to take part in that"

Interview 2 (Female; medium recruitment group)

A minority of GPs said that autonomy was an outdated concept as consultations should be a negotiation with patients; decisions should be taken in conjunction with patients, rather than for patient. Many outside influences affect this negotiation, and a trial is just one of those potential influences. One GP felt that autonomy had no place in modern medicine as it was often used as an excuse to ignore evidence based medicine.

"Clinical autonomy is a pretty old fashioned concept... there are so many kind of outside influences.. its really a negotiation... a clinical trial is just another of the outside influences really. Not a problem"

Interview 8 (Male; high recruitment group)

"clinical autonomy means nothing, patient autonomy is what matters…. Doctors have to be their patient's advocate but too often clinical autonomy is an argument for not following evidence based medicine… nothing to do with being the patient's representative, that's some funny idea that as a doctor you are entitled to your opinions whatever"

Interview 12 (Female; medium recruitment group)

8.5.3 GP Motivation, Experience and Understanding

This theme looks at GP understanding and experience of BAFTA. It covers their reasons for taking part, experience of participating, their understanding of trial processes, and their comments on the very practical aspects of the study, including suggestions for improvement.

8.5.3.1 Motivations for Taking Part

Having discussed their feelings towards the study question, GPs were then asked why they decided to take part in BAFTA. Most GPs alluded to the reasons already discussed, importance of the study, relevance to the practice, and the shift in practice to management of AF in primary care. However, a variety of other reasons also contributed to the decision. A minority of GPs wanted to take part because they had a personal interest in the topic area, or an interest in taking part in research as part of their career development.

"I thought it was an interesting topic, erm, I think that's probably sort of the attraction"

Interview 3 (Female; medium recruitment group)

"I was quite excited cause I had always been keen on medicine for the elderly …. my appraisal was saying oh ever thought of doing any research…. Yeh, when the right thing comes along"

Interview 11 (Male; high recruitment group)

One GP felt that it was an interesting question that was relevant to his practice, but said he did not have a specific interest in the question and felt that he knew the answer anyway,

"it wasn't a burning question that was interesting to know the answer to, mmm, I must admit… I thought, well, I would probably know the answer anyway"

Interview 4 (Male; low recruitment group)

Many GPs decided to take part in BAFTA because they felt that it was a study that would be beneficial either to their patients or to their practice, or both. A few GPs said that it would give them an opportunity for better identification and monitoring of their AF patients, or would force them to make a considered opinion about warfarinisation for all of their AF patients.

"it gives us an opportunity to improve the care for our patients with AF as well, because we'll, we'll see them and monitor them and actually identify maybe new patients as well because of screening"

Interview 10 (Male; medium recruitment group)

"the trial pushed us into putting more people onto warfarin who we wouldn't have done otherwise…. We were waiting to be pushed…. we were quite glad to get pushed"

Interview 5 (Male; medium recruitment group)

A substantial minority of the GPs discussed the timing of the study as contributing to its relevance. For some, this was the relevance of the topic, as practices were beginning to work on their disease registers at the time, and management of AF was one element of this. For others, it was the timing for more personal reasons, for example, a practice decision to participate in more research, or a personal desire to do something new.

"at the time we were just starting to get our disease registers in order….. it was just all sort of relevant at the time"

Interview 3 (Female; medium recruitment group)

"I needed something to get my teeth into"

Interview 6 (Male; low recruitment group)

"we had a clinician and a key nurse ready to embrace something which slightly challenging"

Interview 13 (Male; high recruitment group)

Altruism was cited by a minority of GPs as a factor contributing to their decision to participate. One GP linked this feeling of altruism to the low level of reimbursement on offer to practices for carrying out the study. Another GP described how none of the GPs in the practice were academics, so involvement in an academic study was something that was liked.

"a bit of altruism I guess, it wasn't the money, that's for sure."

Interview 7 (Male; small recruitment group)

"none of us are academics….so I think that was that feeling about it, this has got a feel for it that's quite good"

Interview 6 (Male; low recruitment group)

Although not directly mentioning altruistic motivations, two GPs said that the tone of the initial invitation letter influenced their decision to participate. For one GP, the initial letter was given as his only reason for agreeing to participate.

"you had a very pleading letter (laugh) so you were desperate…. Pleading letters work, yes"

Interview 8 (Male; high recruitment group)

*"We had a nice invitation, a nice letter, yeh oh ok, we will do that… you write to people nicely they do it, demand you don't get…. (*KF so it was purely a nice letter?) *yeh, nice letter"*

Interview 4 (Male; low recruitment group)

The level of reimbursement available to the practice for taking part was also a subject raised by GPs when asked about their reasons for participation. Although the majority of GPs were not interested or involved with finance, as it was the domain of the Practice Managers, most

described reimbursement as being a facilitator that enabled them to take part. The level of payment available in BAFTA was designed to enable practices to free up staff time to carry out the required work, but was not sufficiently high for practices to make a profit. Without reimbursement, studies would rely solely on enthusiastic GPs who were willing to carry out the trial in their spare time. One GP said that while the money may not influence the decision to participate, trialists need to be clear at the outset what is available, because that may influence the practice's ability to become involved.

> *"if there had not been reimbursement then the practice would have said if you want to do it then you do it in your own time basically"*
>
> Interview 8 (Male; high recruitment group)

> *"I think that is going to be quite important really …. We have an agreement so anything done out of GMS[1] time they (the practice nurses) will get that. So it needs to be quite clearly identified"*
>
> Interview 2 (Female; medium recruitment group)

Study training also contributed to the decision about whether or not to participate. A small number of GPs said that they were impressed by the initial presentations, and that this fed into their decision. However, the standard of training did not influence one GP who felt that the study was something they had decided to be involved in anyway.

> *"I must have been quite impressed cos I came back and said well I think we ought to do that"*
>
> Interview 6 (Male; low recruitment group)

[1] GMS is the General Medical Services contract. It describes the services GP surgeries provide to their patients under contract with the National Health Service and determines the level of funding each practice receives from the NHS

"I think that was quite well presented… but again we were quite keen so I think you could probably have had a really bad trial I say we would have continued on with it"

Interview 13 (Male; high recruitment group)

If local training had not been available, then some GPs would not have considered participating. Additionally, the face-to-face nature of the session was an important factor for a significant majority; training via DVD or the internet would have put many off taking part.

"for us to sign up to it, it kind of helps that the training sessions were local, if it had been a lot further afield one would have thought twice about it"

Interview 11 (Male; high recruitment group)

The final area discussed by GPs that influenced their decision to participate was practicalities. Just under half of the GPs felt it would be straightforward to carry out in their practice, partly because they see this particular age group regularly anyway.

"it seemed you know, quite easy to do because those particular age people we tend to see… so it didn't seem difficult to set up a system whereby we could take their pulses"

Interview 1 (Female; high recruitment group)

It was perceived by the majority as an easy study to do, with support and back up readily available, and one GP said that it would not be too time consuming.

"there seemed to be a lot of back up and support with it"

Interview 15 (Male; medium recruitment group)

"it interested me cos it looked like quite an easy study"

Interview 16 (Female; small recruitment group)

"it didn't seem to be too time onerous"

Interview 8 (Male; high recruitment group)

8.5.3.2 Overall Experience

Most GPs enjoyed participating in BAFTA, and commented that they thought it was well organised and well thought through, which made it easier for them to carry out the required work. Many felt that the workload overall was not a problem, though two commented that it was front loaded and it would have been impossible to maintain that pace for the duration.

"it seemed quite hectic in the early stages, you know it calmed down quite a lot. I don't think we could have continued at that pace"

Interview 2 (Female; medium recruitment group)

Most GPs expressed disappointment in the number of patients they actually recruited, and felt that there was a large workload for the number of patients they enrolled. One GP commented that he felt guilty about the number of patients he recruited in relation to the amount of money the practice was paid.

"we did put a lot of work in, we did, and then it was a bit disappointing to only have a few actually"

Interview 14 (Female; small recruitment group)

"it did seem like quite a bit of money for what was one patient…. I do feel guilty about it all… sorry we didn't get any more"

Interview 4 (Male; low recruitment group)

A minority of GPs commented about how it was different to the usual work done in general practice, more structured. Some said this was a welcome change, while others described the process as tedious.

"this formalised repetitive way of doing things is sort of the antithesis of what you do in normal general practice… and that is quite refreshing and it stays refreshing"

Interview 8 (Male; high recruitment group)

"the actual recruitment part was a little bit tedious just really, just getting, identifying the patient, and sending quite a lot of paperwork to fax machines"

Interview 13 (Male; high recruitment group)

Many commented on some unexpected benefits for the practice of participating. Over half of the GPs commented on the ways in which BAFTA improved patient care. Some practices, for example, developed protocols for dealing with AF patients, others introduced in-practice warfarin monitoring clinics in part as a result of taking part in BAFTA. Two GPs found that asking repetitive questions over time allowed them to keep track of changes in patients in a way that would not normally be possible.

"in a way it helped us…look at peoples atrial fibrillation…and create a protocol of what we were going to do"

Interview 8 (Male; high recruitment group)

"it's because of it (BAFTA) from that came our sort of, probably setting up the warfarin clinic to a certain extent"

Interview 14 (Female; small recruitment group)

"It did help us which hasn't been done before, looking at how a patient may have been on warfarin and over time just get gradually more muddled and may well be at risk of taking medication wrongly"

Interview 13 (Male; high recruitment group)

8.5.3.3 The BAFTA Study Team

Overall, most GPs felt that the study team provided a good level of support throughout the trial. Many commented that the team was easily accessible, always available to answer queries and ran the study to a very high standard.

"they run quite all of them to very high standards as we came to expect from the beginning"

Interview 13 (Male; high recruitment group)

"people were accessible and able to give you an answer"

Interview 6 (Male; low recruitment group)

A small minority of GPs commented that they would like more feedback about trial progress, as they felt a little out of touch over time. However, the most appropriate way to keep in touch was unclear. The team sent regular update newsletters to GPs, but a few GPs could not

remember them. Others were unsure as to their benefit, and a few felt that they were beneficial so long as they were kept brief.

> *"you do kind of feel in limbo, you are doing all this stuff and then you wonder what is happening the other end, but I suppose until the trial is complete there is no feedback on anything useful really"*
>
> Interview 8 (Male; high recruitment group)

Many GPs commented that the confidence they had in the research team helped engender a feeling of security while participating. However, one patient was mis-diagnosed with AF and therefore incorrectly randomised into the trial. This GP said that this was a bad experience for both her and the patient, and that the incident dented her confidence in the team. This did not detract from her experience of participating, but did ensure that she took more responsibility for study processes.

> *"where this mistake was made and it would have been better if that hadn't been made…. If I took part in another one would be erm, I suppose it just bear that case in mind and think where the weak spots may be"*
>
> Interview 3 (Female; medium recruitment group)

8.5.3.4 BAFTA Training

The influence of training on decisions to participate has been discussed in section 8.5.3.1. This section will address the impact of the training session on trial participation. Overall, training was perceived as a useful and enjoyable exercise. Most GPs felt that it provided a

good case for the need of the trial and demonstrated that the workload and timescales had been well thought through.

> *"a well put together case as to why the trial is being done and a clear erm, you know that every stage of it had been clearly thought through…. I think it was well done"*
>
> Interview 3 (Female; medium recruitment group)

The majority of GPs felt that they came away from the training session well prepared to carry out the trial, and filled with enthusiasm. However, although stating she felt prepared, one GP did comment that it is possible that she did not come away with the right skills to recruit patients.

> *"I enjoyed it…its going to be brilliant, there'll be hundreds (of patients) ... but maybe the other thing, in retrospect is maybe you know, that it wasn't enough to give me the skills to get them on to it"*
>
> Interview 14 (Female; small recruitment group)

8.5.3.5 Practicalities

Identification of New Cases of AF

Practices were asked to identify new cases of AF by taking a patient's pulse when they attended the surgery; reminders (either paper or electronic) in patient records were used to ensure this was done. The majority of practices regularly highlighted the pulse screening at staff meetings to ensure it did not get forgotten. All GPs said that the system worked well, although one GP commented that it may have been more difficult if the practice had been larger. Another GP talked about the importance of the order in which computer prompts are

activated to minimise the risk of people ignoring them. For GPs entering the study towards the end of the recruitment period this area was not discussed, as identification of new patients was not carried out systematically; only existing AF patients were considered.

> *"those* [pulse reminders] *got managed well in consultation ... being just a small practice, if we'd had more people it would have been more intrustive"*
>
> Interview 6 (Male; low recruitment group)

> *"the sequencing of where things are in the computer record is terribly important if you want people to do things"*
>
> Interview 1 (Female; high recruitment group)

Patient Selection

When describing how they decided on which patients to invite to participate, the majority of GPs said that they made the decision for all potentially eligible patients in the practice, but would discuss patients they were unsure about with the patient's regular GP. All GPs followed the exclusion criteria, but some excluded patients for other reasons, for example, frailty or those in nursing homes. A few GPs said that they may have taken how they felt the patient would react to the invite into consideration.

> *"if you felt that as their GP they were really not up to participating in the study then that was ok to do, and we had a few of those. Either in terms of physical infirmity or mental infirmity, yeah, or cussedness."*
>
> Interview 8 (Male; high recruitment group)

"I don't think I sort of thought oh well, they're a stroppy so and so, so I won't invite them… you can never answer for subconsciously"

Interview 9 (Male; high recruitment group)

Consent Process

Consent was carried out during a clinic appointment with both the GP and the nurse; the GP was responsible for gaining informed consent. Some GPs described the stepwise nature of the process, with consent starting at the point where the patient's pulse was taken, culminating in the full consent for participation, and felt that this was a good approach for the patients. A few practices telephoned the patient after they had been sent the information sheet to discuss the study with them, and to organise a clinic appointment; one GP talked about how they explained to patients that they needed to discuss the study with them during this telephone conversation.

"a telephone call to say look I'm involved in a clinical trial, we think this is very important and erm, we'd like to talk to you about it"

Interview 1 (Female; high recruitment group)

"I didn't go through the original consenting, it was the practice nurse who did that when she did their ECG… I then got consent I think when they came back in having been diagnosed with AF"

Interview 3 (Female; medium recruitment group)

Patient Follow-ups

Patient follow up forms were provided in the form of a booklet which some GPs said was a useful format, allowing referral to the paperwork from the previous appointment. Keeping

track of follow up due dates was difficult, and most GPs relied upon reminders sent by the study team. Keeping them timely, especially during the holiday season was difficult, and one GP said that they did not know what to do with a patient who was late or who had missed a follow up.

> *"difficulty getting it timely… they might not ring for 2 or 3 weeks… and then I might be on holiday or whatever… I started to go by your letters that used to come reminding us….. I became a bit confused….. you kind of lose track of it a little bit so I think the letters were really helpful"*
>
> Interview 10 (Male; medium recruitment group)

8.5.3.6 Understanding

Generally there was good understanding both of general trial principles and BAFTA specific procedures. Most GPs understood the important basics of BAFTA (for example, eligibility) although patient withdrawal was often poorly understood. Patients were not withdrawn from the trial because they were no longer taking their allocated medication, but GPs would often confuse this with withdrawal.

> *"One lady we took out the trial because…. The nurse became increasingly concerned that she was sufficiently forgetful that she wasn't sure she should be taking her warfarin"*
>
> Interview 1 (Female; high recruitment group)

There was a mixed level of understanding about the uncertainty principle in relation to trial eligibility; although the majority understood that they needed to be unsure about the best

treatment for an individual patient, many did not seem to understand that patients also needed to be uncertain as to which treatment they wanted. Patients with a strong preference should not have been entered, but this was not always the case.

> *"There was one person who was happy to go into the trial but did not want warfarin, so he went in and got aspirin"*
>
> Interview 9 (Male; high recruitment group)

Almost all GPs had a good understanding of the need for randomisation, often discussing the need to prevent the results being confounded by other factors. A minority talked about the need to avoid selection bias. One GP seemed to confuse randomisation with blinding and used the two terms interchangeably when talking about how randomisation was explained to patients.

> *"you randomise a trial which means that nobody knows, erm people doing the trial don't know what you're taking, and that I would use yes like the toss of a coin…. And sometimes I'd use the word blind if they obviously, if I felt they werent understanding"*
>
> Interview 1 (Female; high recruitment group)

8.5.3.7 Suggestions for Improvement

GPs made a number of suggestions that would help to ensure that practices could carry out the research as effectively as possible. Most re-iterated the need to keep workload to a mimimum and keep the data collection forms as succinct as possible; flexibility in who can carry out the work was also considered essential by one GP.

"it would be a barrier you would insist on a doctor doing it. You want as many people as possible to do it because otherwise it starts to limit it"

Interview 1 (Female; high recruitment group)

Over half felt that it was important to keep the practice enthusiastic; communication was considered central to this. Effective feedback from the study team was cited as one way this could be achieved; newsletters were felt to be useful, so long as they were not too long or too often. A minority of GPs would have appreciated practice specific feedback, for example, giving them information on how many patients they had screened or ECG'd.

"you do feel a little bit sort of out on a limb… so its [newsletters] quite good in that sense…. Keep it short though cause I havent got time to go through lots of stuff"

Interview 2 (Female; medium recruitment group)

"you will know.. how many we looked at and ECGs we did and actually that would be quite interesting"

Interview 12 (Female; medium recruitment group)

There were a number of suggestions to maximise recruitment and retention. One GP mentioned the mobility of patient populations, and felt that consideration of effective ways of ensuring newly registered patients were included would help; improved use of IT systems to provide reminders was one potential way to achieve this.

"increasing mobility of patients... patients coming in and patients leave so I think that's what we got to look at really.....IT things, I think

"*that worked well because as soon as that clinical indication came up it just popped up... I think that's good"*

Interview 2 (Female; medium recruitment group)

One GP highlighted the need to inform local consultants about the study, because some gave patients conflicting advice, making it harder for patients to continue their involvement in the trial.

"We did have a few incidents that people came back and say you know they [consultants] *had a go at me again because I'm in fibrillation and I'm on aspirin...I wonder whether maybe the local consultants almost had to be got together in the beginning and told face to face... it did cause some anxiety that they were being told conflicting things"*

Interview 11 (Male; high recruitment group)

Final suggestions to improve recruitment including the potential to allow patients to see their own GP, and consideration of the region you recruit in depending on the population of interest.

"I might have done it that they see their doctor they normally saw... in hindsight perhaps if we had done that we might have got better enrolment"

Interview 6 (Male; low recruitment group)

"some of the guys had come from Torbay and Torquay, which is retirement-ville, so if they wanted elderly people, then well you know, coming down here would be a good place to start"

Interview 7 (Male; small recruitment group)

8.6 Patterns of Experience

The data were examined to identify whether any differences in opinions or experiences existed between different groups of GPs. The value of this process could be potentially limited by the fact that only 17 interviews were carried out. However, previous research has successfully identified important patterns in the data despite a small number of interviews.[169] It was decided to examine the data for patterns as it may prove useful to determine whether any exist that could provide any explanation as to why some GPs recruited more successfully than others.

Differences were found between the recruitment groups across all three main themes, and these will be presented in this section. No patterns between demographic factors were identified: this may be due to the small sample size, although data saturation was achieved so it is hoped that this is not the case. It may also be due to the lack of very small practices in the sample. It is possible that patterns may have been identified if these practices had been represented.

8.6.1 Patterns Between the Different Recruitment Groups

As described in Section 7.2.1 GPs were grouped according to the proportion of their eligible patients that consented to participate in BAFTA (See Table 14, page 134). To reiterate, GPs recruiting more than 60% of eligible patients were classed as high recruiters; those recruiting 40-60% of eligible patients as medium, less than 40% were considered low recruiters, and

GPs who deemed less than five patients to be eligible were classed as small recruiters. Differences in attitudes and experiences between these groups were found in a number of different areas.

8.6.1.1 Risk and Responsibility

Differences in attitudes towards the study question were found. GPs in the high recruitment group seemed to have a more clear-cut attitude towards the importance and relevance of the study than those in the other groups; all high recruiting GPs placed emphasis on these aspects. Those in the middle and small groups also discussed the importance of the study, but were more ambiguous. For example, some said that although it was important, they felt that they already knew the answer anyway. The low recruiters discussed the clinical appropriateness of the study, but were less vocal about its importance; these GPs either did not mention importance, or were unclear as to whether they thought it was important or not.

Differences in attitudes towards the study drugs were also found. When asked how they felt about the study question, the high group described the benefits and weaknesses of both study drugs. The other recruitment groups also discussed the trial drugs, but placed more emphasis on the dangers of warfarin and less on the balance of risks and benefits of both. All these groups discussed the trial drugs spontaneously. The low recruitment group did not discuss the drugs at this point. When asked directly how they felt about the drugs, all GPs in the low group stated that they had no problem with either drug, but would also discuss how they felt safer with aspirin rather than warfarin.

There were also differences in attitudes towards entering patients into trials. In the high, medium and small recruitment groups, most GPs were happy with the concept of including patients in trials. One GP said he did not like it because it “put upon” patients, but recruited

anyway because the evidence was needed, while others felt it was good for their patients because patients enjoy participating in trials. Most GPs qualified their statements; they were less comfortable with new drug trials, as they felt these pose more risk to their patients, they wanted the trial to be important and to benefit their patients. The low recruitment group, however, were more concerned. They too differentiated between the risks of new drug trials and trials of more established treatments, but were generally more concerned about the risks associated with involving their patients in trials.

When asked about the ethics of randomisation, all recruitment groups discussed their concerns with drugs company trials, and how it depends upon what the patient is being randomised to. All groups discussed the perceived link between finance and recruitment in drugs company trials, and questioned the scientific basis for some of these studies. However, for the low recruitment group, this was all that was said about the ethics of randomisation. The other groups went into much more detail. All other groups discussed the importance of treatment uncertainty in relation to the ethics of randomisation; there must be no evidence in favour of one treatment over the other. All other groups also related ethical randomisation to patient consent. It was considered ethical if patients were fully informed and were aware of their right to withdraw. GPs in the high recruitment group alone felt that it would be more unethical to carry out trials without randomisation due to the risk of bias, or to continue to use existing treatments without knowing which one was most appropriate, than it would be to randomise patients.

Again, there were differences in attitudes between the recruitment groups when discussing responsibilities towards patients. GPs in the high, medium and small recruitment groups said that they would feel responsible for events happening to patients as part of a trial, in a similar

way to how they would feel responsible outside of trial conditions. Some GPs in these groups felt that the trial actually took some of that responsibility away from them as long as they were happy with the trial parameters at the outset. In contrast, the GPs in the low recruitment group talked about how it would be difficult to 'square' if something happened to a patient in a trial. One GP said he would not feel responsible, but felt that patients would blame him anyway. In the high, medium and small groups many GPs felt that the responsibility lay more with giving or changing medications than with involving patients in trials; events happening to patients because of their disease were seen to absolve the GPs of any responsibility. In the low group, this aspect of responsibility was not raised.

8.6.1.2 Doctor/Patient Interaction

When asked about how they discussed the study with patients, GPs in the high recruitment group described how they felt that patients often knew what they wanted to do with regard to the trial before they came to the appointment. They usually established what the patient understood and wanted to do, and tailored their explanation based on this. The patient information sheet was used as a starting point and the discussion was tailored to individual patient requirements. They often used simple analogies to describe randomisation, for example, like the toss of a coin, or the 'computer decides'. The low recruitment group appeared to be more prescriptive and would read through the information sheet with the patient; the simple analogies for trial concepts like randomisation did not appear to be used.

There were different feelings about the impact of trial involvement on the doctor/patient relationship between the recruitment groups. All GPs in the high recruitment group felt that involving their patients in trials did alter this relationship, though they all felt that it was a positive change: they felt that it helped them to get to know their patients better. Of those who recruited 40-60% of their eligible patients, most felt that it either did not influence the

relationship, or if it did, it was, again, a positive change. There was a different attitude amongst the low recruiting GPs however, as they expressed more concern about whether patients were wondering about the GP's motivation for involving them in trials and felt that this would have a negative influence on their future relationship.

8.6.1.3 GP Motivation, Experience and Understanding

GPs were asked about their motivation for participating in BAFTA. Some of these centred around the study question and its relevance and importance: these have already been discussed in section 8.6.1.1. However, GPs often cited other reasons for taking part and there were, again, differences between the groups. GPs in all groups except for the low recruiters gave multiple reasons for taking part. The reasons given were discussed in more detail in section 8.5.3.1, but included benefits for their patients or the practice; the appropriate timing of the trial, altruism or personal interest. Their decision to participate was often multi-faceted with a variety of factors contributing. In contrast, the low recruitment group gave fewer reasons. One GP was interested because he was looking for something new to do, therefore the timing was right; he considered it mainstream research, not something that was novel or especially high risk. Another participated as a result of a nice invitation letter and stated that no other factors influenced the decision.

Some GPs spontaneously discussed the unanticipated benefits of participating in BAFTA and again, there were differences between the groups in the way this was discussed. GPs in all groups except the low recruiters discussed it in terms of improved care for their patients. They felt that involvement in the trial enabled and encouraged the practice to introduce protocols and systems for the better identification and management of patients with AF. Improved GP understanding of the condition and how to manage it was also cited as a benefit of participation; the increased exposure to AF and warfarin management allowed them to

automatically know what factors to consider when they identified new AF cases. In contrast, the low recruitment group stated only that BAFTA allowed them to identify additional patients with AF.

The final pattern that emerged from the data with regard to differences between the recruitment groups were their opinions about issues affecting the recruitment of patients. Again, there were distinctions between the low group and the others. Most GPs talked about how they found it difficult to identify eligible patients, how it was harder to include patients already receiving treatment for their AF than it was to enrol new AF patients, and how GP discretion in deciding eligibility allowed them to exclude patients that they felt would not want to participate. Low recruiting GPs, however, highlighted different concerns. They felt that the need for randomisation impacted negatively on recruitment, felt that their patients prefer to be left alone and discussed how difficult it is for practices to engage with research.

8.6.2 Demographic Patterns

There was only one pattern of opinions that emerged from the data when looking at demographic factors (for example, GP age; practice size; gender) or the year of practice involvement in the study, and this related to GP age and their thoughts about the study question. Older GPs (those who qualified before 1981) placed more emphasis on the importance of the study to their patients than their younger counterparts. Older GPs all placed emphasis on the importance of the question; they felt that it was important to find out the most appropriate way to treat older patients with AF. They were concerned about the risks to their patients of AF and of warfarin. Younger GPs tended to describe the trial in terms of its clinical appropriateness and relevance to practice; the discussion was less directly related to the benefits for patients. It did not appear that younger GPs were less concerned about their patients than older GPs, but they did seem to phrase their attitude to the study question

differently, and this may have communicated itself to patients. This will be discussed in more detail in Chapter Nine.

8.6.3 Within-case Analysis

When looking at the views of individual responders, only one trend was found. GPs that had cited benefits to the practice or their patients as a factor influencing their decision to participate tended to have similar views on various aspects of the trial. For example, they all felt that BAFTA was a low risk trial, and none had any concerns about the ethics of randomising patients to different treatments, providing that they were happy with the trial at the outset. None were worried about the doctor/patient relationship, and felt that trial involvement either had no impact on this relationship, or else there was a positive effect. Most felt equally responsible for patients outside trial conditions as they did for patients that they had entered into a trial; they felt more responsible for changes to medication than for trial enrolment. Furthermore, all cited two or more benefits to the practice of taking part in BAFTA.

In contrast, GPs that did not include the benefits to their patients of participation in their reasons for participation had more mixed opinions on these other aspects of trial participation. A few considered BAFTA low risk, but most had more concerns about the risk associated with putting their patients into trials. About half of them felt that trial involvement would impact negatively on the doctor/patient relationship, and some were concerned about the potential for restriction on their clinical autonomy. Additionally, only a few of these GPs discussed any benefit to the practice of participation: those that did cited fewer reasons than those GPs who had identified the potential benefits at the outset.

Although there are a number of limitations to this study (discussed in detail in Section 9.4), many of these findings are supported by previous research. Concerns about the risks posed to patients of involvement in trials, the potential impact of participation on the doctor/patient relationship and the feelings of responsibility that doctors have for their patients have been raised by clinicians in the past. However, previous research looking at these areas has all been carried out in a secondary care setting, mainly with regard to cancer treatment trials. Until now it was not clear whether these concerns related to primary care based RCTs: these findings demonstrate that the concerns remain applicable. Interestingly, some of the attitudes demonstrated by GPs differ to those reported to be held by specialists, especially with regard to concerns about the impact that the trial discussion could have on the patient relationship. What remains unclear is why these concerns differ and whether they can be mitigated, therefore improving both practitioner and patient recruitment.

This study also found that factors that motivate GPs to take part in research seem to influence patient recruitment. This is not a new finding. As discussed in section 2.3.3.1, three survey studies also found that motivations were associated with recruitment. Interestingly, the factors previously found to be influential were often different from those found in this study, so it remains unclear what motivators impact on a clinician's ability to recruit patients for research. It is also not clear how or why these factors should impact in this way. However, if considered in the context of theoretical concepts of motivation, specifically Self-determination Theory (SDT), these findings may begin to make sense: the relevance of SDT will be discussed in section 9.3. Understanding of how these complicated and often interlinked perceptions impact on patient recruitment may allow researchers to identify ways in which to overcome these potential barriers.

Another interesting area identified during the interviews was the idea that the act of participating in BAFTA improved patient care. Many GPs felt that their understanding of the condition and its management improved as a consequence of participation, and that this resulted in better care for their AF patients. This is not a finding that has been discussed in previous literature with regard to research, although there is evidence that Stroke Units provide better care for patients with acute stroke than they receive in general wards. Participation in research is a central tenet of Stroke Units, and it is possible that this contributes to their expertise.[170] This finding could be potentially useful for researchers looking to recruit GPs to participate in their trials and will be discussed further in section 9.4.

A number of interesting and potentially useful points have been identified during the interview phase of this PhD. These will be discussed in more detail in the next chapter. Interview results will be discussed in relation to recruitment to RCTs, and placed in the context of both existing literature and, where appropriate, to existing theoretical concepts.

Chapter 9: Discussion of Interview Results

As previously stated, this chapter will discuss the findings of the interviews in more detail. Strengths and limitations of the qualitative study will also be discussed.

9.1 Demographic Factors

Only one demographic factor previously reported as being associated with patient recruitment (Chapter 5) was found to have any bearing on difference in GP attitudes: GP age. Older GPs demonstrated a slightly different attitude towards the trial than their younger counterparts and it may be that this impacted on their ability to recruit. For example, older GPs talked about the important, worthwhile nature of the study question and its importance to their patients, whereas younger GPs placed more emphasis on the clinical appropriateness and relevance to practice of the question. It may be that these perceptions transferred to the patients during the consent discussions, and as a result, patients of older GPs also considered the study to be important and were therefore more willing to participate. It was not possible, however, to identify any differences from the interview data in the way that the trial was explained to patients; more specific detail about how the consent process was conducted would be needed. Older GPs may have been more likely to recruit because older patients view older GPs more positively than they do younger ones.[171] It may be down to the attitude of older GPs towards older patients: research has shown that GPs feel more responsible for their older patients than they do younger ones.[118] It may be that older GPs feel that responsibility differently to younger GPs, and this was reflected in their ability to recruit. It is unclear how much practical use this finding may be to trialists, as a GP's age cannot be changed. Site recruitment could be targeted towards older GPs, but care would need to be taken to ensure that this did not introduce any bias into the study population.

9.2 Risk and Responsibility

Almost all GPs talked about their concerns about the risks associated with involving their patients in trials and concerns they have about the medications under examination. Risk is linked to motivation in that some GPs stated that one of the reasons they agreed to participate is they felt that BAFTA was a safe, well monitored trial that was not looking at potentially risky new drugs. However, risk was also a central theme running through many of the decisions GPs took with regard to the trial. This section will examine the potential impact of perceived risk on both GP involvement and patient recruitment.

The findings from the interviews imply that the perceived risks of a trial play a large part in a clinician's decision as to whether or not to participate. A significant majority of GPs described how they felt that BAFTA was a low risk trial, using established drugs with known risks and this factored into their decision to take part. Most also highlighted concerns about drug company funded trials, feeling that they posed more risk to patients as they tend to involve novel treatments with unknown or unquantifiable risks. It is likely that these opinions would not apply to all GPs: the sample included in this study would have been self-selecting, in that they all chose to take part in non drug company funded research. Many GPs are happy to take part in research testing newer drugs. The literature review did not identify any publications that directly linked the perceived risk of the trial with a clinician's decision to participate. It may be that this has not previously been identified because the majority of prior research has been limited to survey studies or retrospective analyses of individual trial recruitment processes; the questions relating to risk and the decision to become involved may not have been asked. It could also be possible that concerns about risks have been masked by other concerns. For example, Salmon et al explain that non-participation due to lack of time actually masks deeper concerns, such as giving researchers access to their patient records.[104] It

may be that when GPs describe the relevance of a trial, they have actually factored in the risks that they feel their patients may be exposed to and decided the potential risks make it not relevant enough to take part.

The findings of this study imply that a clinician's perception of the level of risk posed by a trial has an impact on their ability to recruit once they have decided to take part. Previous recruitment research has not identified this as a factor directly influencing recruitment. However, research about risk communication may shed some light on why this may be the case. It is known that there is often a discrepancy between individually perceived risk and medical understanding of risk as communicated by GPs: personal experience, interpretation and cultural context impacts on an individual's evaluation of risk.[172] Furthermore, how a person is informed about risk allows for different personal interpretations of the same facts.[173] The Royal Statistical Sociey recommends that greater use is made of numerical as opposed to verbal descriptions of risk, although this was aimed specifically at first-in-man trials.[174] Risk communication research indicates that a GP's personal perception of the risk of an activity, together with the way that is communicated to patients, will impact on an individual patient's perception.[172] It is possible, therefore that both the GP and the method of communication will influence a patient's willingness to participate in research. However, one study examining risk communication to a hypothetical trial of pain relief medication in patients with cancer or arthritis found that this was not actually the case: although patients demonstrated a clear preference for being given risk information numerically, the format of presentation was not found to impact on their willingness to participate in a trial.[175]

These mixed findings may be explained by the complexity of a trial situation. Clinicians in this scenario need to explain a variety of risks and benefits: the risks posed by the disease in

question; the risks and benefits of the treatments in question; and the risks and benefits of trial involvement. It is possible, therefore, that alterations to the format of risk presentation from verbal to numerical is too simplistic to be the complete solution. The difficulties are exacerbated further; for a trial, GPs need to explain the balance of risks and benefits across two different treatments. A minority of GPs in BAFTA said that they felt it was difficult to achieve balance in this respect.

The need to cover prescribed requirements[38] during the informed consent discussion adds a further level of complexity to the recruitment process. While it is obviously vital that patients understand research they are being asked to get involved in, and are satisfied with the risks and requirements associated with the trial, it is important that they are given the information in an unbiased manner, and that they receive the information in a manner that they are comfortable with. A law review of informed consent states that current guidelines, 'Instead of providing a channel of communication between physician and subject… is a lifeless entity responsible for a large portion of the misunderstanding existing between these two parties'.[176] Ziker concludes that an understanding of how the patient perceives and reacts to risk can help to revise the existing consent process, allowing it to better achieve its objectives of protecting volunteers while encouraging participation.[176] To understand how individuals interpret risk, GPs must first identify 'where the patient is coming from'.[177] It is not enough that researchers believe that the justification for a trial is good, as people also react to risk in a subjective manner.

The risk perception concept has a number of principles that may help overcome some of the difficulties encountered during the trial consent process. The theory as put forward by Ropeik et al, states that people are more comfortable with risk if they have chosen to be exposed to it,

so clinicians should emphasise the voluntary nature of participation. They also recommend that clinicians emphasise the control that patients retain over their participation, underlining the fact that they can withdraw at any time.[178] This concurs with the feelings of many interviewed GPs, who felt that it was important that they emphasise to patients their ability to change their mind at any point. Highlighting the benefits to patients of participation is not only a requirement of GCP, but also encourages people to enrol. Clinicians should explain the benefits both to the individual and to society of their participation. Although personal benefit is the prime motivation of participants, altruism, or the benefit to society, also encourages people to enrol.[178] Trust also helps potential participants to be less fearful of the risks posed by trials.[178] This can be advantageous to clinicians who have developed a relationship with their patients, as a bond of trust has already been formed. It may also account for why GPs seem to cite fewer concerns about the impact on the doctor/patient relationship than their colleagues in secondary care. GPs can get to know their patients over a long period of time or a large number of consultations, and this enhances both GP feelings of responsibility towards their patients[118] and patient trust in their GP.[153] It may be that specialists develop a different relationship with their patients, thus making it more difficult for them to broach the subject of research participation.

The findings of the BAFTA interviews, combined with the literature surrounding risk perception, indicate that participation could be improved while still respecting ethical principles, if peoples' reactions to risk and how the method of communication influences this were better understood. GPs taking part in research all receive GCP training prior to taking consent. However, this focuses on the ethical requirements of consent and does not touch on the practical aspects of the process. As stated by one GP who recruited fewer patients than expected, the study training was very useful, but with hindsight may not have furnished her

with the necessary skills to recruit patients. It is possible, therefore, that clinicians, patients and trialists could benefit from the development of a training course that would enable them to carry out the consent process in the optimum manner.

9.3 Motivation

Having discussed the impact of risk perception on trial recruitment, it must be acknowledged that improvements in the consent process are not likely to solve all recruitment problems. Clinicians have many different reasons for taking part in research, and in this thesis, differences in motivations between low and high recruiting GPs were found (See section 8.6.1.3). As discussed, low recruiting GPs cited few motivations for taking part, whereas all other GPs gave multiple reasons. Low recruiting GPs participated because they either wanted to do something new and this was felt to be low risk to their patients, or because they were asked "nicely" to get involved. Others discussed perceptions about the study question, potential benefits to the practice or patients, timing, personal interest and altruism. Although little work has been done to determine the impact of clinician motivation on recruitment, these findings do support the findings of studies that have been carried out in this area (See section 2.3.3.1). The impact of motivation will be discussed further in section 9.3.2.

9.3.1 Self-Determination Theory and Work Motivation

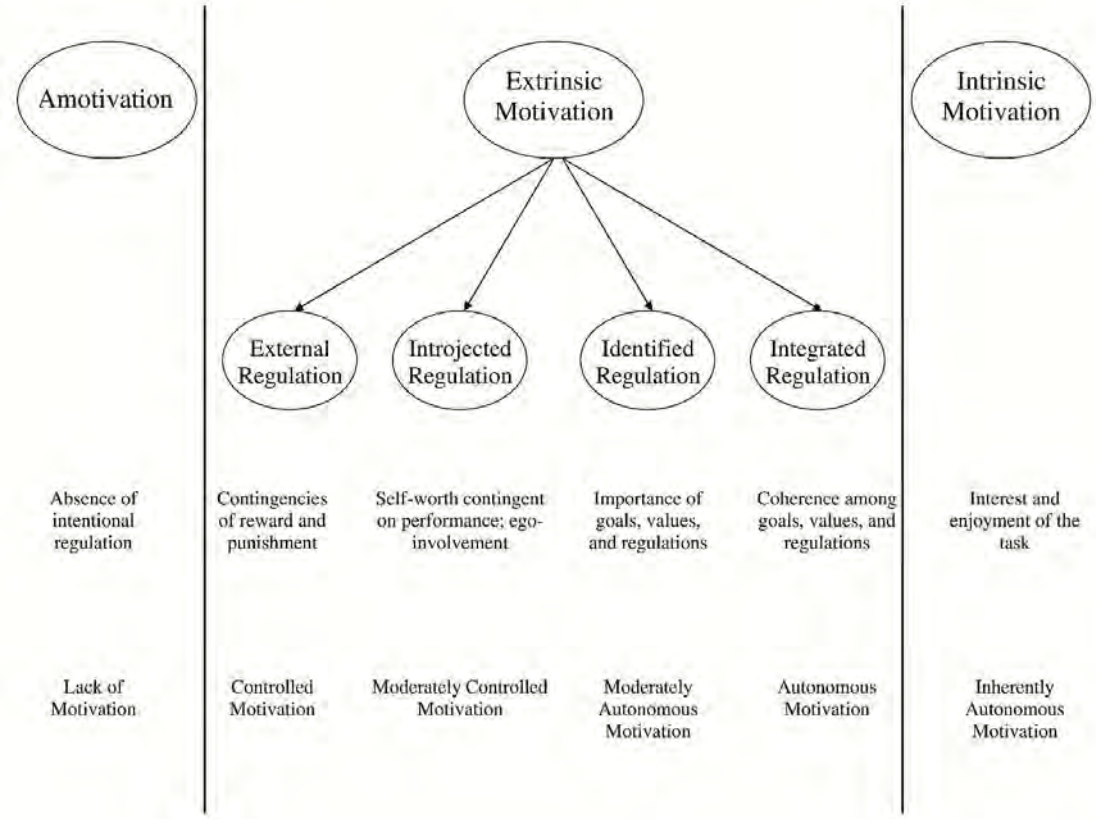
The impact of motivation on recruitment also fits with theoretical concepts about motivation, particularly the Self –determination theory and work motivation.[179] Self-determination theory (SDT) is based on Cognitive Evaluation theory (CET) which was amended to be relevant to motivation in the workplace.[179] CET defines different types of motivation: intrinsic and extrinsic. Intrinsic motivation is that which comes from within, so people engage in an activity because they find it interesting and derive satisfaction from the activity itself, for example, 'I work because I enjoy my job'. Extrinsic motivation is that which comes from

outside and involves tangible or verbal rewards; satisfaction comes from the reward rather than from the activity itself, for example, 'I work because I get paid'. Intrinsic motivation is the most important type in terms of positive work outcomes because it enhances performance; interesting tasks that people choose to do often get carried out better than other tasks. CET suggests that it is possible to manipulate extrinsic motivations so that they become intrinsic, for example, by giving people increased autonomy over how they carry out tasks. Implicit in the model is the idea that the intrinsic and extrinsic motivations add together and result in total job satisfaction. The problem with this is that subsequent research demonstrated that different motivations do not add up, rather they are both positively and negatively interactive.[179] A further concern when relating the theory to the workplace is that not all work tasks can be intrinsically interesting, so strategies to enhance intrinsic motivations are often not feasible. In response to these concerns, SDT was developed.[179]

SDT distinguishes between autonomous and controlled motivation. Truly intrinsic motivation is completely autonomous as it is driven from within. Extrinsic motivation can vary in the degree to which it is autonomous versus controlled. Activities that are not intrinsically motivating need a link between doing the task and a desired reward, or avoidance of an un-desired consequence, for example, 'I work because the boss is watching'. However, SDT argues that controlled motivation can be internalised, therefore becoming autonomous, or intrinsic. For example, values are accepted and no longer require external controls, so 'I work even though the boss is not watching'.

Internalisation is an overarching term for three different processes: introjection; identification; and integration. Introjection is a relatively controlled form of motivation: a process is carried out, but not accepted as an individual's own regulation. The control comes from outside, for example, people feel pressured to behave in a specific way to feel worthy. Identification is classified as a partly autonomous extrinsic motivation, and arises when a behaviour is more linked to personal goals or identities. For example, a nurse may carry out uninteresting tasks, such as bathing a patient, because they understand it is for the good of the patient, and they strongly value patient comfort. Integrated regulation is a truly autonomous extrinsic motivation and is when a behaviour is an integral part of a person's personality. For example, a fully integrated nurse would see the importance of maintaining their patient's health and would carry out uninteresting tasks to achieve this, but would also demonstrate their caring tendencies in areas of their life outside work, caring for elderly relatives for example. Despite being autonomous, this type of motivation would remain extrinsic because interest in the task in question is not the primary motive. These distinctions are demonstrated visually in figure 14 (page 213).

Figure 13: The Self-Determination Continuum*[179] (P 336)



*The self-determination continuum showing amotivation, which is wholly lacking in self-determination; the types of extrinsic motivation, which vary in their degree of self-determination; and intrinsic motivation, which is invariantly self-determined. Also shown are the nature of the regulation for each and its placement along the continuum indexing the degree to which each represents autonomous motivation.

SDT says that how the workplace is organised can influence how people are motivated, but does not suggest that changing motivations means people have to pass through each stage of the model to become fully autonomous. Rather it proposes that under optimum conditions, people can fully integrate a task or regulation that is either new or previously only partially integrated. Gagne and Deci argue that work climates that promote satisfaction in the three

basic psychological needs (competence, autonomy, and relatedness, i.e. an activity relates to a personal need) by encouraging full internalisation of extrinsic motivations will result in important work outcomes, including: maintained behaviour change; effective performance; positive work related attitudes.[179]

9.3.2 BAFTA and Self-Determination Theory

SDT and the concepts of intrinsic and extrinsic motivation may shed some light on why some GPs were low recruiters and others managed to enrol more. The theory argues that the more autonomous the motivation is for a task, the better that task is carried out. This section will examine the reasons that GPs gave for participating to determine whether the high recruiting GPs were more autonomous than their lower recruiting counterparts. To achieve this, the reasons given need to be classified according to the self-determination continuum. This is not straightforward, as the questions were not asked of GPs with this theory in mind. Therefore, some subjective interpretation of motivations cited has to be carried out.

Only one factor seems to come under the umbrella of inherently intrinsic motivation: interest in research. Citing an interest in taking part in research per se implies that there is something about the process itself that interests some GPs, and they carry out the tasks required because they enjoy them. This is validated somewhat by the fact that GPs giving this as a reason also described how they enjoyed the overall experience, and that the processes they followed were a refreshing change from their usual work patterns. Only GPs in the high and medium recruitment groups cited interest in research as a motivation for participation.

A number of motivations were given that are categorised as controlled motivation, the most controlled form of extrinsic motivation. These include the remuneration available for taking part, participation in research because it is beneficial for their career, and the tone of the initial

invitation letter: all are based on some form of external reward for participation. GPs citing these reasons came from across the recruitment categories, rendering it unclear as to whether extrinsic motivations do in fact result in poorer work outcomes. However, when looking at these motivations in context, it becomes clear that most GPs gave these reasons in conjunction with a variety of other more autonomous reasons, although GPs in the low recruitment group gave only extrinsic reasons.

Other motivations fall into the remaining categories, identified and integrated regulation, but are more difficult to categorise between these two groups as specific questions with this in mind were not asked during interview. These include: altruism; personal interest in the topic; importance and relevance of the study question; and benefits to the practice or patients of their participation. These factors were considered to demonstrate values of GPs, who feel responsible for their patients and want to give them the best treatment possible. They place importance on and show integration of goals and values. For example, GPs will behave in their patients' best interests because they are driven by keeping their patients as healthy as possible, even if they do not find the specific tasks they undertake intrinsically interesting. Interest in the study question is distinct from interest in research per se, because it is driven by a desire to answer a question that is relevant to their patient care. Similarly, many cited benefits to their patients for the same reasons: answering such a pertinent question would enable them to ensure the best care for their patients.

A central part of SDT is that different types of motivations result in different work outcomes: more autonomous motivations result in better outcomes. This argument seems to apply in this instance. It would be expected that GPs in the low recruitment group would cite fewer autonomous and more controlled motivations for participation and it does seem that this is

actually the case. GPs in the low recruitment groups gave only controlled reasons for taking part, such as a nice invitation letter. GPs in all other groups gave more varied reasons. While many said remuneration, benefits for their career, or the tone of the initial invite factored into their decision to take part, these were invariably cited as part of a wider variety of reasons. All GPs in the higher recruitment groups also gave at least one autonomous motivation, and often more. Those in the highest groups cited only autonomous motives, and especially focussed on the potential benefits for their patients.

The discovery of patterns of motivation within the BAFTA interview data is supported both by existing literature pertaining to patient recruitment and by theoretical concepts of motivation in the workplace. As discussed in section 2.3.3.1, prior research has highlighted the fact that motivation was associated with recruitment rates, although it was not clear why this was the case. However, BAFTA motivations that relate to recruitment differ slightly from those found by De Witt et al;[34] they found that interest in the question was not associated with recruitment, while BAFTA indicates that those with an interest were in the higher recruitment groups. It is possible that De Witt et al did not capture the nuances of interest as they gathered their data in a survey; structured questions may not have allowed them to identify different reasons underlying interest. GPs may be interested in a question because they have a particular interest in that area of medicine, or because they see a lot of patients with the condition in question and feel it would benefit them to identify the best form of treatment. The reason why GPs find the study question interesting could therefore be an important factor that influences their recruitment rates, and this was not identified by De Witt et al.[34]

The current findings, together with prior research, indicate strongly that motivation for participation does have an impact on recruitment rates. Although BAFTA goes some way to

identifying what motivates doctors to take part in research, the evidence so far does not explain why motivations may have this effect. However, when related to SDT, the reasons why motivation may influence recruitment rates become clearer. SDT theorises that more autonomous motivations lead to improved work outcomes, and this supports the BAFTA findings; GPs citing only controlled motivations all recruited less well.

Unfortunately, the evidence so far does not explain how these motivations actually make a difference. It may be, as posited in SDT, that intrinsically motivated GPs gain more job satisfaction, and so find more time to incorporate the extra workload into their daily schedule. It could also impact on how they communicate the trial to their patients. GPs who think that the study is important may communicate these feelings during the consent process. It is possible that GPs who only participated because they were invited politely were unable to convey the benefits of the trial in the same way that their more autonomously motivated colleagues could, and this impacted on patient willingness to participate. These findings are potentially useful for researchers: identification of what motivates individual GPs to participate could enable them to select their sites based on the likelihood that clinicians would recruit high proportions of patients. It could also influence the training given by trialists to recruiters. Further research needs to be carried out in this area to determine whether or not motivations in the context of trial recruitment could be manipulated. For example, if benefits to patients increase intrinsic motivation, a greater part of the training could be devoted to highlighting these benefits.

9.4 Unanticipated Benefits of Participation in BAFTA

The majority of GPs described changing attitudes towards the BAFTA trial question over the four year recruitment period. (See section 8.5.1.5) Most described how they were less concerned about the risks of warfarin in the elderly at the end of the trial than they were at the start. In some cases, this was attributed to a general change in attitudes to prescribing warfarin. Although the guidelines for prescribing warfarin to this patient population did not change during the recruitment period, there was a general increase in willingness to prescribe warfarin throughout the medical community. A minority of GPs felt that guidelines had changed, and that they were now almost expected to prescribe this drug unless there were clear reasons not to. One GP was unsure whether the guidance was underpinned by research, and felt that the BAFTA results would be interesting, particularly if they were at odds with the NICE Guidance.[180] As no new guidelines were published during the recruitment period, it is not clear why this changed attitude arose. It is possible that other factors influenced this change in attitude. More practices, for example, were involved in warfarin monitoring for their patients. A few GPs discussed how they felt that because of this, there were more safety procedures in place to ensure that patients took their warfarin correctly towards the end of the trial than there were at the beginning, and this gave them the confidence to consider prescribing the drug to a wider group of people.

The interesting finding with regard to this change in attitude over time, however, was the perception of a number of GPs that participation in BAFTA had improved their practice. A significant minority of doctors during interview described the unexpected benefits of taking part. They explained that they felt that their knowledge of AF had developed, enabling them to identify more patients with the condition. They also felt that their understanding of how to best manage the condition had improved, to the point where, as one GP said, he doesn't have

to think about what to do with these patients, he just knows (Interview 5). A minority of GPs described how they felt more confident prescribing warfarin in this age group, sometimes because their increased exposure to the drug increased their confidence in prescribing it, or because involvement in the trial had underlined the fact that chronological age was less important than physical age. One GP explained that participation in the trial had demonstrated to her that patients can often incorporate regimes such as warfarin management into their lives with few problems, in contrast to her assumption that they would all find it problematic. All GPs discussing this change in attitude felt that this improved knowledge and understanding resulted in better care for their patients, and that they had not expected this benefit from the trial. This finding has not been discussed in previous research, but does resonate with the experience of Stroke Units caring for people with acute stroke. Examination of the organisation of acute stroke care found a significant correlation between quality of stroke care and research activity. The authors conclude that this suggests that well organised stroke care facilitates patient involvement in research, and/or that participation of stroke units in research improves services and therefore patient care.[170]

This information has the potential to be useful for researchers in a number of ways. Firstly it could be used to encourage larger numbers of GPs to incorporate research into their everyday workload than currently do. The majority of successful recruiters cited benefits to their patients as a factor influencing their decision to take part in research, and most discussed how they felt that their own improved knowledge and understanding resulted in improved care for their patients. Researchers and Research Networks may be able to utilise this information to encourage more sites to consider involvement, thus reducing the current issues often encountered when trying to engage adequate numbers of sites. Initial information given to GPs could highlight the specific benefits to the patients of practice participation in a particular

study, including the potential benefits to their patients of improved GP knowledge and understanding gained through research participation. Further research needs to be carried out to determine whether research involvement actually does have a positive impact on service provision or quality of care. However, if this were proved, involvement in research could potentially be one way of carrying out continuing education for GPs and could result in research becoming a mainstream activity that is more central to the role of GP, rather than being the domain of those GPs who are interested enough to add research to their already demanding workload.

9.5 Limitations

One of the limitations of this study is the fact that compromises had to be made in the sampling process (See Section 7.2.1). As discussed, these compromises resulted in no interviews with GPs from the very small practices (those with one or two GPs). This may explain why there appeared to be no differences in attitudes between GPs in smaller practices and those in larger practices, despite this being a significant predictor of consent. It is feasible that GPs in very small practices have different attitudes to those described in this study. For example, they may have better knowledge of their patients. Unfortunately, it was not possible to collect data to test this.

The time constraints that led to compromises in the sampling process also resulted in compromises with the analysis (See Section 7.2.2). The data could not be analysed concurrently with data collection which meant that unexpected findings from early interviews would not be followed up in subsequent interviews. However, as only one researcher carried out all interviews, follow up of unexpected findings was carried out in an informal manner. For example, the perceived differences between drug company funded trials and those testing established drugs were raised by GPs in the early interviews, and the researcher ensured that

the subject was explored during those that followed. Although formal concurrent analysis in theory might have resulted in identification of additional aspects of GP experience, in practice subsequent analysis did not identify any areas that should have been incorporated in the later interviews. Therefore, it is unlikely that the lack of concurrent analysis had a detrimental impact on this study.

Another potential limitation is the small sample size. Although 19 GPs were interviewed, only 17 transcripts were included in the analysis. It is possible that more interviews would have uncovered opinions that could have better explained the statistical differences identified in chapters five and six. However, data saturation was achieved, with no new ideas emerging from the data after interview 15.

The limited time available to some GPs for the interview may have resulted in less rich data. Some of the interviews lasted only 30 minutes and it was not possible to cover the whole topic guide in any depth in this amount of time. A decision was taken during these interviews to cover all areas in less depth rather than focus on a smaller part of the topic guide and probe further into responses, unless an individual raised different issues from those already identified. Despite the lack of depth, however, some interesting and unexpected findings came out of the interview data which add knowledge to the current literature.

There are a number of issues inherent in this study that may have influenced the nature of the data that were collected. Firstly, there was a time lag of approximately 12 months between the end of patient recruitment and the start of interviews. This may have resulted in recall bias influencing the data, especially when discussing the specific detail regarding trial implementation. However, GPs had continued to follow up their patients until approximately

three months prior to interview and were therefore still very engaged with the trial. Furthermore, large parts of the interview covered generic trial issues, for example, the ethics of randomisation, and these were unlikely to have been affected by the time lag. Secondly, the interviews were carried out by the BAFTA trial manager, which may have influenced GPs willingness to discuss their genuine thoughts regarding the trial. Although this may have influenced the discussions in some cases, it is unlikely to have had a significant impact upon the data; a number of GPs were explicit about negative aspects of their experience, while others stated that they were aware of the interviewer's role in the trial, but that this would not deter them from giving honest responses to the questions.

It is also possible that these findings relate only to primary care based trials of cardiovascular disease in older people. Although qualitative research does not aim to be generalisable in the same way as quantitative research, the usefulness of the findings is limited if they apply only to such specific circumstances. The findings of this study are only likely to apply when considering older patients for trial entry: a number of areas discussed may differ when considering younger patients. For example, many GPs described concerns about the ability of older patients to understand and accept trial concepts, or discussed worries about the impact of co-morbidities or polypharmacy on eligibility. A few also described their feelings of responsibility towards their older patients. These concerns may be less acute when considering a younger patient population and would need to be researched in trials incorporating a different patient group. However, a number of issues raised are likely to apply to primary care based trials regardless of their disease area. The influence of motivation for participation on recruitment, for example, could equally apply to research looking at other conditions. If GPs recruit well because they value the benefits of participation for their patients, this is also likely to apply to studies that are not in the field of cardiovascular

medicine. Additionally, some of the more generic trial issues raised could also apply to other conditions. For example, the ethics of randomisation or the limitations posed by practice and/or study workload are not limited to cardiovascular medicine.

Chapter 10: Conclusions

Previous chapters have discussed the findings of the individual projects that make up this thesis. This chapter will summarise the key findings from earlier chapters, discuss the extent to which the original aims of the thesis (Section 1.3) have been addressed and will bring together the earlier findings to provide some overall conclusions. The novel findings from this work will also be highlighted.

10.1 Objective One: What Practice or Practitioner Factors Influence the Recruitment of Patients to Primary Care Based RCTs?

The first aim of this thesis was to conduct a review of the literature pertaining to primary care based RCTs to determine what practice or practitioner factors influence patient recruitment, and to identify methods that can overcome any identified issues (See Chapter Three). The review successfully achieved this aim, providing a comprehensive overview both of factors that may affect recruitment, and of approaches designed to overcome difficulties. (See Table 18, page 225). Although systematic reviews of recruitment methods have been done before,[2,3,4,16,35,49] this is the first review that synthesises the literature specific to both primary care and practitioner (as opposed to patient) considerations. It provides primary care based trialists with a detailed account of difficulties encountered during other RCTs, and the approaches that researchers use to alleviate them. It identifies both similarities and differences between the issues faced by researchers carrying out trials in a primary care setting and those encountered in secondary care. It demonstrates, for example, that recruitment of sites appears to be more problematic in primary care than it does in secondary care, and suggests approaches trialists can employ to minimise the difficulties, as shown in table 18. It also highlights apparent differences in concerns that GPs have when conducting research than those held by

Table 19: Overview of Factors Affecting Recruitment and Recruitment Approaches

Factor	**Problem**	**Solution**
Interest in the study question	Lack of interest discourages site participation	Emphasise the relevance and benefits of the trial both to the practice and to patients Consider different approaches for initial contact with practices
Negative attitude towards research	Not perceived as professionally relevant GPs have no responsibility for conducting research	Emphasise the benefits of participation Encourage cultural changes to raise the research profile
Ability to carry out the study	Lack of time Lack of suitably trained staff	Minimise workload Maximise flexibility of who can carry out study tasks Ensure all staff receive appropriate training
Personal Relationships	Exploitation of personal/professional relationships may encourage participation	Use a 'local champion' Use of peers to send site invitations
Participation of academic research groups	The literature is mixed. This may have a positive or negative impact on recruitment	Develop good working relationships

specialists, for example, worries about the impact of trial involvement on the doctor/patient relationship. However, the review also determined that the existing literature is problematic, with much of the evidence being conflicting or unproven in RCTs of recruitment approaches. There remains a need for further research in this area (See Chapter 11).

10.2 Objective Two: Do Patient and/or Practitioner Factors Predict the Likelihood of a Patient giving Consent to BAFTA?

The second objective of this thesis was to identify whether patient and/or practitioner factors predicted the likelihood of a patient to give consent to the BAFTA study. Although a number of studies examining GP factors influencing recruitment were identified in the systematic review, most of these focussed on the referral of patients to trials and it was not clear whether referral translated into actual recruitment.[25,77] While this may be useful for studies where clinicians refer patients to researchers who then complete the recruitment process, it is of less use for trials where clinicians are carrying out both identification and recruitment. Only two studies considered the influence of GP demographic characteristics on recruitment and neither found any association.[57,95] However, the analysis of recruitment to BAFTA demonstrated for the first time that practice and practitioner factors (GP age; practice size) can predict the likelihood of an eligible patient giving their consent to take part in a trial (See Chapter Five). It is possible that sample size accounts for the difference between the analysis of BAFTA and the previous literature, which surveyed 98 and 186 clinicians as opposed to BAFTA, which included 262 GPs. A further difference is that the BAFTA analysis focussed on the 1740 patients who were considered eligible for the study by their GP. As described in Chapter Five, these patients all attended an appointment with their GP to discuss trial entry,so the analysis was able to explicitly explore the direct impact of GP characteristics on the consent process.

The results have implications for primary care trialists. When recruiting sites, those most likely to recruit effectively could be selected, focussing on smaller practices or older GPs, for example. However, this would have untoward consequences as it would automatically deny a large number of GPs and patients access to research, and may also inadvertently limit trial applicability by selecting a non-representative set of sites to participate. Therefore, this is not an approach that would be recommended unless future research proves it to be appropriate. Despite this, lessons can still be learned from this study. For example, it would be logical to assume that larger practices would recruit more patients because they have a larger patient pool to begin with, and researchers may be tempted to focus on these sites. However, these findings indicate that trialists should use this approach with caution; it may be more sensible to ensure that smaller practices are actively encouraged to participate, as they may include a more resource effective number of patients.

10.3 Objective Three: Did Protocol or Procedural Changes in BAFTA Influence Patient Recruitment?

The next aim of the thesis was to use BAFTA to determine whether protocol and procedural changes impacted on patient recruitment, or whether the target number of patients was only reached because of the increased number of participating sites (See Chapter Six). The systematic review identified a number of studies that described how patients were recruited to different trials, and explored different strategies for identifying and enrolling patients (See Table 6, page 43). Many trialists employ a variety of techniques to improve patient recruitment, including minimisation of GP workload,[75] simplification of study protocols[82] or increasing the number of participating sites.[18] However, most of the studies were descriptive and it is unclear which, if any, of these approaches successfully improved recruitment. The analysis of BAFTA data was the first to demonstrate that procedural and/or protocol amendments can be associated with improved recruitment rates, lending tangible support to

the recruitment guidance given in the literature.[17] However, although this is an important finding, this analysis does not help trialists to pinpoint which changes were responsible for the increased recruitment. Improved understanding of how and why these factors influence recruitment would ultimately lead to better trial design, enabling maximisation of recruitment from the outset and reducing the need for costly and time consuming amendments.

10.4 Objective Four: What Were GPs' Experiences of Recruiting Patients to BAFTA?

Having synthesised the existing literature in this subject area, and identified various factors that influenced recruitment to BAFTA (practice and practitioner factors; procedural and protocol changes), the next aim was to understand the experience of GPs who recruited to BAFTA. It was anticipated that this understanding would provide some explanation for the differences identified in the BAFTA analysis. The interview topic guide was based upon the findings from the prior work. For example, broad trial questions (i.e. attitudes towards randomisation; equipoise or risk; motivations for participation) were informed by the systematic review, while BAFTA specific questions (i.e. attitudes towards the training sessions; practical aspects of the trial; understanding of trial processes and protocol) were informed by the findings of the earlier BAFTA analyses.

Despite some limitations (See Section 9.5), the interview study did shed some light on the earlier findings. As discussed in section 9.1, there was a difference in attitude towards the study question between older GPs and their younger counterparts, which may have translated into recruitment rates. However, as it is possible that older GPs recruited better because they have a different relationship with their older patients than do younger GPs,[171] it may be that studies with a younger patient population would have different findings. No patterns were found in the data when considering the other factors previously found to be associated with

recruitment (practice size; year of recruitment), so it remains unclear as to why they influenced recruitment.

Although this study had limited success in providing explanations for the associations identified earlier, it did identify other areas that may have important implications for patient recruitment. Many interviewed GPs indicated that workload, simplicity of the protocol and appropriateness of eligibility criteria were all important considerations that affected their ability to carry out the study, lending support to the existing evidence.

Many BAFTA GPs talked about how improved knowledge and understanding gained through participation in BAFTA led to better care for their patients. As discussed in section 9.3, there is an argument that taking part in research improves the service offered to patients, and therefore improves patient care. The findings of this study imply that benefits to patients of participation may be an important factor that influences both a GPs willingness to participate, and their subsequent ability to successfully recruit. Whilst this theory has not been proven, the information is potentially useful for researchers. GP participation could be encouraged by tailoring the initial invitations to emphasise the potential benefits to patients. Recruitment could be optimised by exploring the ways in which participation could improve their management of the condition in question during clinician training sessions.

One of the most interesting findings of this interview study relate to the patterns in the data that exist between GPs with differing levels of recruitment (See Section 8.6.1). GPs in the low recruitment group, for example, had a different perception of risk and responsibility, and more concerns about the potential impact on the doctor/patient relationship than their counterparts who recruited more successfully. Some of these issues have been discussed in the existing

literature, although the focus has tended to be on the impact these considerations have on the initial decision to participate (See Table 6, page 43). Only three studies discussed these problems in relation to their willingness to recruit or refer patients.[77,89,97] However, they did not relate their findings to ability to recruit, rather they identified these as potential areas of concern. This analysis has demonstrated for the first time that these issues actually affect a clinician's ability to enrol their patients. However, why these perceptions may influence recruitment remains unclear. It may be that these feelings influence the informed consent discussion. For example, those with a low tolerance for risk may subconsciously impart their feelings to patients during the process. Similarly, GPs who perceive the benefits to patients of participation could also inadvertently convey these feelings to their patients.

The impact of motivation to participate on subsequent ability to recruit is another important finding of this study. Only one previous study has examined the impact of motivation upon recruitment[34] and its findings differed slightly from the results of the BAFTA interview study. They found that the study question was not associated with recruitment, whilst the findings of this interview study suggest that differing attitudes to the study question result in different recruitment success rates. However, it is possible that different methodologies account for the apparently contradictory findings; De Witt et al carried out a survey of research active clinicians.[34] Questions were therefore pre-defined, and there was no ability to delve further into why the topic under investigation inspired clinicians to participate. In contrast, this study was able to uncover the reasons why the trial question promoted involvement. The methodology employed here does not allow causation (i.e. importance of the study question leads to high recruitment rates) to be proven. However, this is the first study that has identified reasons why the question motivates GPs to participate (e.g. the question is important because it improves care for my patients), and to relate these detailed motivations to

ability to recruit. Furthermore, it is the only study to consider the impact of motivations in relation to self-determination theory. This theory provides a potential explanation as to the mechanisms that enable motivation to influence outcomes. Consideration of motivation could allow researchers to identify those GPs most likely to recruit high numbers of patients. However, further research needs to be carried out to identify the most appropriate way to utilise this information, and to determine whether motivation is open to manipulation and therefore to improved recruitment.

10.5 Objective Five: How can Patient Recruitment to Primary Care Based RCTs be Optimised?

The final objective was to give recommendations for the optimal recruitment of patients to trials in primary care and to identify areas that would benefit from future research. These recommendations draw upon all aspects of this thesis, from both the systematic review and the original analyses. This objective will be discussed in detail in chapter 11.

10.6 Conclusions in the Context of Primary Care Trials in 2012

The BAFTA study completed recruitment in 2006. In the six years since then there have been some changes to how primary care trials are conducted. The introduction of the clinical research networks has changed, in many cases, how trials are carried out; research network nurses often go to participating practices to enrol patients thus removing the need for individual GP involvement. However, some trials still use GPs to identify and consent patients, which means that the findings of this thesis are still relevant to trials being carried out today. Furthermore, it is possible that many factors that impact on GP recruitment also influence network research nurses; there are often differential recruitment rates between individual nurses. Future research should take this into account.

The regulation surrounding the permissions that are needed to carry out research has also increased significantly. It has become more complex, burdensome and time consuming, with the result that it is very difficult to implement any protocol or procedural changes in a timely manner. The delay caused by the need to gain approvals for these changes has the potential to have a significant detrimental effect on a trial's ability to turn around failing recruitment rates. Therefore, it is even more important for trialists to understand which factors in this study had an impact on the recruitment rates, and why. This would enable them to ensure that protocols were effectively designed in the first instance.

The primary care clinical environment has also changed since BAFTA was actively recruiting. Although disease registers were coming into being during the recruitment phase, the introduction of Quality Outcomes Framework (QoF) in the period since BAFTA ended has formalised this process, with practices being paid directly and specifically for managing certain elements of their patients' conditions. Practices actively identify and manage patients with a range of usually chronic diseases such as stroke. This has the ability to impact on recruitment to trials in different ways. On the one hand, disease registers can make it easier to identify the prevalent population of the disease in question. On the other hand, increasing workload in primary care more generally including QoF may put increased pressure on the time that GPs have available for research. Research participation is not rewarded through QoF, so it remains vital to ensure that practices have other motivations for participating. Again, the findings of this study surrounding the impact of motivation would be directly relevant to this.

In conclusion, the primary care clinical and research environments have changed dramatically since BAFTA was carried out, rendering it even more challenging to carry out RCTs in this

arena. As a result of these increased challenges, it is even more important to ensure that trials can maximise their potential for recruitment. The findings of this study, therefore, are likely to be even more pertinent to 2012 trials than they are to trials carried out in the past.

Chapter 11: Optimisation of Recruitment to Primary Care Based Randomised Controlled Trials

This final chapter of the thesis gives recommendations for the optimum recruitment of both sites and patients to primary care based RCTs, based on current knowledge. As discussed, there remain a number of question marks over the most appropriate approaches to overcome the difficulties. There remains a need for a sound evidence base that would enable researchers conducting RCTs in primary care to achieve patient recruitment targets in the most cost and time effective manner. Therefore, this chapter will also highlight areas which would benefit from further study.

The influences on a trial's ability to recruit fall into two main areas: site recruitment; and patient recruitment. These will be presented in turn. The chapter will then conclude with a discussion of areas that would benefit from future research.

11.1 Guidance for the Recruitment of Sites

The recruitment of adequate numbers of suitable sites is a challenge faced by many trials. This seems to be especially problematic in primary care. The current literature gives advice to trialists on the best way to encourage sites to participate in research. This thesis has provided evidence that supports the existing literature and has also identified some extra factors that have not been considered before. These are summarised in table 19 (Page 233).

Table 20: Guidance for Recruiting Research Sites

Recommendation	Reason	Literature/thesis
Minimise practice workload	High workload discourages participation	Literature/Thesis (Chapter 8)
Be flexible about which staff are able to carry out study specific tasks	Ability to delegate may enable better accommodation of workload, therefore encouraging participation	Literature/Thesis (Chapter 8)
Consider carefully the manner in which practices are approached	Personal contacts may increase site recruitment but decrease patient recruitment	Literature
Give realistic estimations of payments and workload	Enable practices to make informed decisions. Practice participation may reduce but false expectations may result in practice inability to carry out the work	Literature/Thesis (Chapter 8)
Highlight the benefits to patients as well as to the practice, of participation in the study	Appreciation of benefits to patients may increase site participation and have a positive impact on subsequent patient recruitment	Thesis (Chapter 9)
Many sites decide to participate after attending training. Reiterate the question relevance and benefits of participation during training	Potentially has a positive impact on patient recruitment	Thesis (Chapter 8)

11.2 Optimisation of Patient Recruitment

Recommendations for optimising patient recruitment, based both on the evidence in the literature and the findings of this thesis are summarised in table 20.

Table 21: Recommendations for the Optimisation of Patient Recruitment

Recommendation	**Reason**	**Literature/Thesis**
Consider GP motivations for participation. Could motivations be amended by giving different information to GPs? Could site be selected based upon motivation?	Motivation potentially impacts upon the ability to recruit patients. GPs who participate because of potential benefits to patients may recruit more successfully.	Thesis (Chapter 9)
Ensure simplicity of trial procedures and protocols.	Keeps workload to a minimum	Literature/Thesis (Chapter 8)
Ensure data on non-randomised patients is collected carefully.	Too much concentration on collection of this data may detract from patient recruitment	Thesis (Chapter 8)
Be flexible about which staff are able to carry out study specific tasks	Ability to delegate may enable better accommodation of workload, therefore encouraging participation	Literature/Thesis (Chapter 8)
Ensure investigators are equipped with the appropriate skills, especially with regard to obtaining consent	Inadequate training may have a detrimental effect on recruitment	Thesis (Chapter 8)

Problem	Solution	Literature/Thesis
Consider Lasagna's Law. Is the disease prevalence lower than estimated?	Increase the number of sites	Literature
Is the study failing to identify potentially eligible patients?	Amend processes to ensure all patients are identified	Literature/Thesis (Chapter 6)
Are the inclusion/exclusion criteria too restrictive?	Amend to protocol to allow more patients to be eligible (if it can be done without being detrimental to the trial)	Literature
Are there delays between study training and recruitment start up?	Staff can lose interest or other activities take priority if the practice is unable to begin when they expect to, having a negative impact upon recruitment	Thesis (Chapter 8)
Can failing sites be supported to improve recruitment or would resources be better focussed elsewhere?	It is possible that sites that are finding it difficult to recruit may be unable improve, dependant upon their reasons for failure	Literature/Thesis (Chapter 6)

Many of the approaches taken to improve recruitment are not based on good evidence. No RCTs to test the above recommendations have been carried out. Some of the recommendations arise from the findings of the interview study described in chapters 7-9, and therefore still remain only potential solutions to the problem of patient recruitment. More

research needs to be carried out in a number of areas and these will be discussed in the next section.

11.3 Future Research

As discussed in section 9.3, GPs motivation for taking part in a trial may influence their subsequent ability to recruit patients. This raises a number of areas for future research.

11.3.1 Does Motivation Influence Recruitment?

Further research needs to determine whether motivation does actually impact on recruitment rates. A prospective study to identify why a GP participates could answer this question. This study should take into account the potential associations between motivation and recruitment.

11.3.2 Can Motivations be Manipulated?

Self-determination theory gives some insight into how motivation may influence recruitment (see section 9.3), indicating that intrinsic motivations result in better work outcomes. The ability to manipulate motivations would potentially have many benefits to researchers. Further research in a number of areas would be beneficial:

- A trial that looks at whether motivations can be manipulated may allow trialists to optimise patient recruitment;
- The most appropriate way to successfully manipulate motivations also needs to be identified. It may be that the initial contact to the practice needs to reflect these considerations;
- Where it is not possible to change motivations, a study to determine whether it would be appropriate to select practices on the basis of the GPs motivation to participate may enable optimal patient recruitment.

11.3.3 Which Protocol or Procedural Factors Influence Recruitment?

A trial testing different ways of implementing an RCT would have the potential to identify what aspects of protocol or procedural changes actually influence recruitment. This would allow trialists to design their trials with the optimum chance of success from the outset.

11.3.4 Does Involvement in Research Improve Clinical Practice?

A study demonstrating that involvement in research improves the care for patients would have two main benefits for researchers. Firstly it would lend strength to the argument that research participation should be an integral part of general practice, potentially increasing site recruitment. Secondly it could enhance patient participation, as benefits of improved care for patients may potentially be associated with improved patient recruitment.

11.3.5 What is the Optimum way to Gain Informed Consent?

When considering the consent process, there are a number of areas that may benefit from further research.

- Previous research demonstrated that the order in which trial arms are presented to patients can influence their decision about participation.[44] Studies to identify how trialists can determine the most appropriate way to describe their trial to patients could optimise patient recruitment.
- Studies to determine whether GPs' perceptions of risks and benefits colours the consent discussion would be beneficial. Further research to identify whether training amendments could ensure that these perceptions do not influence way in which the trial is explained may increase recruitment rates.
- Further research to establish whether specific training for GPs on gaining patient consent for involvement in research, together with identification of the most appropriate format for this training, could have a positive impact on recruitment rates.

11.4 Conclusion

The decision to use mixed methods to address this research question has allowed detailed exploration of the question posed by this thesis. As discussed throughout this chapter, each approach built on the prior findings of the thesis, and informed the next steps. Taken together they have provided a comprehensive overview of the factors that may influence patient recruitment and provided a sound basis for future research into a variety of ways to overcome the issues raised. Use of a single methodological approach would not have provided such an in-depth understanding of this complex subject.

Although the findings of this thesis do not present researchers with proven solutions to the problem of patient recruitment, they do offer useful information that can be taken into account when planning trials. Trialists need to achieve a balance between ethical recruitment of adequate numbers of patients from a population that appropriately answers the research question, and practical aspects of recruitment that will impact on their ability to achieve their aims. Athough this thesis has put forward a number of suggestions to optimise recruitment, the most appropriate way to accomplish this remains unclear.

Appendix One: BAFTA Training Day Agenda

Agenda 2001 Training Session	
Time	**Content**
1.00 to 1.30	Registration & lunch
1.30 to 1.45	Overview of practice manual 1. Contents of the practice manual (investigator/working versions) 2. Practice proforma 3. BAFTA team 4. Protocol
1.45 to 2.00	BAFTA standard operating procedures 1. Practice staff roles 2. Generic SOPS
2.00 to 2.30	**What are CRFs and SOPs?** **DESCRIBING THE PATIENT PATHWAY THROUGH THE STUDY** 1. Identifying patients (case note review & opportunistic screening) 2. ECG clinic 3. Randomisation clinic 4. Patient follow-up
2.30 till 3.30 Parallel sessions	**GP session (1):** 1. Opportunistic screening (CRF2) 2. Input before randomisation clinic (CRF6) 3. Randomisation clinic (CRF7b) - study inclusion criteria/exclusion 4. GP follow-ups (CRF8a-i) 5. Loss to follow-up (CRF12) **PN SESSION (1):** 1. Opportunistic screening (CRF2) 2. ECG clinic (CRF3) 3. Input before randomisation clinic (CRF6, discuss with GP) 4. Randomisation clinic (CRF7a)
3.30 till 3.45	Tea
3.45 to 4.30	**Small group work** GP session (2) PN session (2)
4.30 till 4.45	**Summing up - what happens next?** Getting ready for BAFTA (Section 2) BAFTA practice visit to start study running

Agenda 2003 Training Session		
Session	**Time allocated**	**Time slot**
Registration	30 mins	9.00 to 9.30
Introduction; Rationale & protocol; Cardiological input.	75 mins	9.30 to 10.45
Coffee break	15 mins	10.45 to 11.00
MidReC Information and GCP	40 mins	11.00 to 11.40
HertNet Information	20 mins	11.40 to 12.00
The practice manual	15 mins	12.00 to 12.15
Lunch	45 mins	12.15 to 1.00
Patient consent	30 mins	1.00 to 1.30
Small group work GP session Nurse session	1½ hours	1.30 to 3.00

Appendix Two: Factors Predicting Consent, Family Practice Publication

Family Practice Advance Access published May 29, 2007

doi:10.1093/fampra/cmm019

An analysis of factors that predict patient consent to take part in a randomized controlled trial

Kate Fletcher, Jonathan Mant, Roger Holder, David Fitzmaurice, Gregory YH Lip and FD Richard Hobbs

Fletcher K, Mant J, Holder R, Fitzmaurice D, Lip GYH and Hobbs FDR. An analysis of factors that predict patient consent to take part in a randomized controlled trial. *Family Practice* 2007; Pages 1–7 of 7.

Background. Recruitment targets of patients to multi-centre primary care-based randomized controlled trials (RCT) are often not met. A critical step in the pathway is whether an eligible patient will give consent.

Objective. To assess whether patient, practice or practitioner characteristics are associated with a patient's likelihood of giving consent to participation in a large primary care-based RCT.

Methods. A cross-sectional study of patients from 260 practices in England and Wales who met the eligibility criteria for an RCT of aspirin versus warfarin for stroke prevention and attended an appointment with their GP to consider trial participation. Logistic regression analysis was used to determine which patient and practitioner factors independently predicted whether or not a patient would give consent to take part in the trial.

Results. Of the 1740 patients, 973 (55.9%) gave consent. On multivariable analysis, patient factors associated with increased likelihood of giving consent were younger age, current use of warfarin and year of recruitment to the trial. Patients with a history of transient ischaemic attack, angina or valve disease were less likely to give consent. Practice/practitioner factors that were associated with increased likelihood of consent were smaller practice size (practices with greater than eight GPs as compared with those with one to two GPs, odds ratio 0.40, 95% confidence interval 0.21–0.75) and older GPs.

Conclusions. The strong association of consent with year of recruitment may be due to changes in trial procedures and investigator training. If so, this has important implications for the conduct of future trials.

Keywords. Consent, primary care, RCT, recruitment.

Introduction

Randomized controlled trials (RCTs) are widely accepted as the best way of evaluating treatment effects.[1] A key success criterion for RCTs is that a reasonable proportion of eligible patients are included. This ensures both that sufficient participants are recruited in a reasonable timescale, allowing the trial to meet the study power requirement, and that the recruited cohort is representative of the study population.

Recruitment of patients to RCTs is often difficult, with many studies struggling to reach their targets.[2,3] In multi-centre trials, local clinicians are relied on to recruit patients, leaving the study centre with limited control over recruitment.[4] If clinicians do not recruit enough patients, then studies become more expensive, take longer and fail to achieve their recruitment targets. Primary care-based RCTs often rely on a large number of research sites to recruit patients, and these trials also suffer from problems with patient recruitment. However, reasons for low patient accrual are poorly understood and few methods employed by research teams to improve recruitment are evidence based.[5]

Many reasons are given for poor recruitment, including overestimation of yield from particular sources, inadequate planning and inability to amend recruitment strategies rapidly if recruitment is slow.[6] Extensive literature exists that cites problems with the

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consent process as being a major barrier to recruitment,[2] but these relate mainly to secondary care cancer trials that are likely to have specific problems that do not relate to primary care-based trials looking at other diseases. The literature often focuses on the need to determine patient levels of understanding to ensure that patients have given fully informed consent, but less evidence is available on whether patients have also given fully informed refusal.[7] This is an important issue if researchers are to achieve their targets while ensuring that the right patients both enter and decline trial participation. More understanding of the factors that influence consent is needed so that these can be taken into account when planning future trials.

This analysis is based upon a large primary care-based RCT that aimed to recruit patients aged 75 and over with a diagnosis of atrial fibrillation (AF) to a trial of warfarin versus aspirin for prevention of stroke.[8] Although our recruitment target was achieved, patient entry was slower than anticipated and required a restructuring of our recruitment strategy to achieve study power within a reasonable timescale. To identify reasons for this initial delay and to help inform the design and conduct of future primary care trials, we explored what patient, practice and/or practitioner characteristics predicted whether an individual would consent to take part in the trial.

Methods

The methods of the trial are described elsewhere.[8] In brief, potentially eligible patients were identified through computer searches for AF supplemented by opportunistic screening of the pulse. An electrocardiograph (ECG) showing AF was required to confirm eligibility for the study. One doctor per practice acted as the local investigator for the study. The research team trained investigators in study procedures and Good Clinical Practice over the 4-year period (2001–2004) that patients were recruited. During this time, changes were made both to study procedures and to investigator training (Table 1). Trial procedures were simplified and payments to practices were altered.

Once trained, investigators screened their patients to determine eligibility. The medical records of patients aged over 74 who were found to have ECG confirmed AF were examined for presence of any study exclusion criteria (rheumatic heart disease, history of intracranial haemorrhage, major gastrointestinal haemorrhage in last 5 years, active peptic ulcer, allergy to study medications). If the primary care physician (GP) was in equipoise as to whether or not they should be treated with aspirin or warfarin after review of relevant risk factors for stroke and haemorrhage, the patient was invited to attend a study clinic.[8] Eligible patients were sent a patient information sheet and a letter inviting them to see their primary care physician to discuss trial participation. During this appointment, the patient made the decision whether or not to take part in the study.

TABLE 1 *Changes to the trial procedures*

Criteria	Date of change	Detail of change
Changes to trial procedures	2002	Broadening of inclusion criteria to allow people already on warfarin to be considered.
	2003	Assessment process of patients simplified to shorten time from investigator training to patient recruitment and to reduce investigator workload.
		Payments to practices changed from payment in advance to payment for work carried out.
	2004	Computer searches for AF expanded to reduce need for opportunistic screening, and thus further reduce investigator workload.
Changes to training methods	2003	Training sessions reduced from 8 to 5½ hours.
		New evidence to support study rationale included.[16]
	2004	Training sessions reduced to 4 hours.
		Good Clinical Practice reduced and made more study specific.
		More detail on rationale for study.
		Sessions made more interactive.

This analysis focuses on the 1763 patients from 260 practices in England and Wales who demonstrated that they were willing to consider study participation by attending the study clinic. Information on past medical history and medications was collected from the medical records. Disability score was completed by the patients during the study clinic appointment. Practice and practitioner characteristics were collected in a questionnaire completed by each practice on recruitment to the study. Data on the year that the practice and the patient were recruited to the study and the number of patients attending a study clinic appointment from each practice were available in the study database.

The effect of patient, practice and practitioner factors on patient consent was explored using logistic regression, univariable for factors considered one at a time and multivariable for factors considered in combination. Further multivariable analysis was conducted using a multi-level mixed effects model.

Results

In total, 1763 people attended the study appointment. Twenty-three (1.3%) had absolute exclusion criteria

and so were excluded from this analysis. Of the 1740 included, 51% were male, 94% white, 32% already taking warfarin, 44% already taking aspirin, 9% had a history of transient ischaemic attack (TIA), 6% had a history of stroke and 70% were already known to have AF. The mean age of attendees was 81.9 years (range 74–96). In total, 973 (55.9%) patients consented to be randomized, although there was a wide variation between local investigators in the proportion of eligible patients who gave their consent (0–100%) (Fig. 1).

Patient factors

On univariable analysis, people already on warfarin were more likely to give consent. Patients offered trial entry in 2004 were almost twice as likely to participate as those considered in 2001. Patient socio-economic status also predicted whether or not a patient would consent, although there was not a simple linear association between the quartiles. Patients on aspirin and those with an increased risk of stroke (history of TIA, angina or non-rheumatic valve disease) were less likely to give their consent, as were people aged over 85. There was no significant difference, however, between the two younger age groups (Table 2).

On multivariable analysis taking both patient and practice factors into account, patient deprivation and use of aspirin were no longer significant. All other factors that were significant in univariable analysis remained so with the logistic regression model (Table 2). Patient deprivation was eliminated, as it was strongly associated with the number of practitioners in a practice, the number of patients attending a study clinic appointment and the date that the patient entered the study. Use of aspirin was no longer significant because there was a strong inverse association with use of warfarin. With the multi-level model, the pattern of effects was very similar to that seen with the logistic regression, with the regression coefficients from the two analyses showing a correlation of 0.95. However, as expected, effects were generally less significant. Previous TIA was no longer significant and the significance of valve disease was marginal ($P = 0.06$). Other factors remained significant.

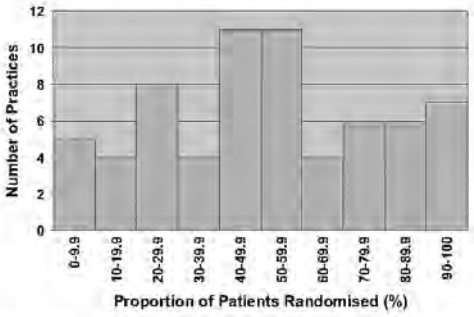

FIGURE 1 *Proportion of eligible patients giving consent, per practice (Practices who saw fewer than 10 patients at study clinic are not included in this figure)*

Practice factors

On univariable analysis all practice factors, with the exception of primary care physician sex, had a significant effect on a patient's likelihood of giving consent. Patients registered with practices who attended study training during 2004 were almost twice as likely to consent as patients in practices who trained in 2001. Similarly, patients in smaller practices were most likely to consent. There was a clear linear association with practice size, with people being less likely to consent as the number of practitioners within their practice increased. Patients in practices where fewer people attended a study clinic were also more likely to consent. Patients of longer practising primary care physicians [those registered with the General Medical Council (GMC) prior to 1975] were also more likely to give their consent.

On multivariable analysis, the year that the practice was recruited to the study was no longer significant, due to its strong association with the year of patient recruitment. All other factors that were significant in univariable analysis remained so (Table 2). With the multi-level model, year of full GMC registration was no longer significant.

Discussion

This is the largest study to look at factors influencing patient consent to a multi-centre primary care-based RCT. We found both patient and practice factors independently predicted whether a patient would consent to take part.

Patient factors

The patient factors may reflect general attitudes towards trials, with understanding and acceptance of issues such as randomization, uncertainty and acceptability of treatment arms playing a part in a patient's decision on whether to participate.[9–11] Many of the patient factors could also be specific to the interventions (warfarin and aspirin) being tested,[3] with patients already on warfarin being more likely to give consent. This presumably reflects the inconvenience and unpopularity of the treatment.[12] Patients with a history of valve disease, angina or TIA were less likely to give consent. This could be due to the impact of perceived illness severity on trial participation,[10] or it may be that these patients had a strong preference for warfarin as they felt that they had more to benefit from this therapy.[11,13] The reduced likelihood of older patients

TABLE 2 *Influence of patient and practice characteristics on patient consent to participate in a randomized trial of warfarin versus aspirin for AF*

		No. (%) giving consent	Odds ratio (95% confidence interval) from logistic regression	
			Univariable	Multivariable[a]
Patient factors				
Sex (n = 1647)	Female	443 (58)	1.00	
	Male	530 (60)	1.09 (0.90–1.33)	
Ethnicity (n = 1682)	White	913 (56)	1.00	
	Non-white	29 (64)	1.44 (0.77–2.67)	
Age (n = 1721)	75–79	385 (59)	1.00	
	80–84	395 (58)	0.98 (0.79–1.22)	1.11 (0.87–1.42)
	85+	193 (49)	0.68 (0.53–0.88)	0.75 (0.56–0.99)
Index of Multiple Deprivation (quartile) (n = 1643)	1 (least deprived)	338 (54)	1.00	
	2	224 (54)	0.99 (0.77–1.26)	
	3	192 (52)	0.97 (0.71–1.19)	
	4	150 (65)	1.55 (1.14–2.12)	
Disability score (Rankin) (n = 1680)	0 (least disabled)	173 (54)	1.00	
	1	265 (58)	1.19 (0.89–1.58)	
	2	296 (60)	1.29 (0.97–1.71)	
	3	187 (53)	0.97 (0.72–1.31)	
	4–5	26 (45)	0.70 (0.40–1.22)	
Already on warfarin (n = 1628)	No	592 (55)	1.00	
	Yes	381 (70)	1.88 (1.51–2.34)	1.47 (1.13–1.91)
Already on aspirin (n = 1604)	No	527 (63)	1.00	
	Yes	407 (53)	0.64 (0.53–0.78)	
Polypharmacy (on five or more drugs)	No	559 (55)	1.00	
	Yes	414 (57)	1.07 (0.89–1.30)	
Diabetes (n = 1645)	No	844 (59)	1.00	
	Yes	129 (60)	1.06 (0.79–1.42)	
Previous TIA (n = 1643)	No	893 (60)	1.00	
	Yes	80 (52)	0.72 (0.52–1.01)	0.65 (0.45–0.94)
Previous stroke (n = 1639)	No	914 (60)	1.00	
	Yes	59 (56)	0.85 (0.57–1.26)	
Epilepsy (n = 1622)	No	951 (59)	1.00	
	Yes	7 (39)	0.44 (0.17–1.13)	
Previous myocardial infarction (n = 1643)	No	870 (60)	1.00	
	Yes	103 (56)	0.85 (0.62–1.16)	
Angina (n = 1637)	No	818 (61)	1.00	
	Yes	155 (52)	0.67 (0.52–0.86)	0.64 (0.48–0.84)
Heart failure (n = 1640)	No	783 (60)	1.00	
	Yes	190 (56)	0.83 (0.65–1.06)	
Non-rheumatic valve disease (n = 1635)	No	905 (60)	1.00	
	Yes	68 (52)	0.70 (0.49–1.00)	0.61 (0.41–0.90)
Hypertension (n = 1643)	No	445 (59)	1.00	
	Yes	528 (60)	1.03 (0.84–1.25)	
AF status	Already known	683 (56)	1.00	
	New case	290 (55)	0.97 (0.79–1.19)	
Year patient attended study clinic	2001	96 (3)	1.00	
	2002	184 (44)	0.71 (0.50–1.00)	0.70 (0.48–1.02)
	2003	252 (54)	1.06 (0.75–1.50)	1.00 (0.68–1.47)
	2004	441 (66)	1.75 (1.25–2.43)	1.76 (1.18–2.61)
Practitioner and practice factors				
Practitioner sex	Female	246 (56)	1.00	
	Male	727 (56)	1.01 (0.81–1.25)	
Year of full GMC registration	<1975	195 (63)	1.00	
	1976–1980	206 (53)	0.67 (0.49–0.91)	0.63 (0.44–0.90)
	1981–1985	195 (54)	0.70 (0.51–0.95)	0.70 (0.48–1.02)
	1986–1990	238 (62)	0.96 (0.71–1.31)	1.08 (0.74–1.56)
	>1991	139 (47)	0.53 (0.39–0.74)	0.61 (0.41–0.90)
Size of practice (no. of GPs)	1–2	98 (75)	1.00	
	3–4	262 (62)	0.55 (0.36–0.86)	1.13 (0.68–1.89)
	5–6	335 (54)	0.40 (0.26–0.61)	0.65 (0.39–1.07)
	7–8	225 (51)	0.34 (0.22–0.53)	0.63 (0.38–1.07)
	>8	53 (42)	0.25 (0.15–0.42)	0.40 (0.21–0.75)
Year of recruitment to study	2001	310 (50)	1.00	
	2002	98 (47)	0.86 (0.63–1.18)	
	2003	262 (57)	1.31 (1.03–1.67)	
	2004	303 (66)	1.95 (1.52–2.50)	

TABLE 2 *Continued*

		No. (%) giving consent	Odds ratio (95% confidence interval) from logistic regression	
			Univariable	Multivariable[a]
Number of patients attending	1–5	249 (69)	1.00	
	6–10	286 (49)	0.44 (0.33–0.57)	0.46 (0.33–0.64)
	11–15	220 (53)	0.50 (0.37–0.67)	0.54 (0.38–0.78)
	16–20	104 (57)	0.59 (0.41–0.86)	0.82 (0.51–1.30)
	>20	114 (56)	0.58 (0.40–0.83)	0.77 (0.49–1.21)

n = 1740, unless specified.
[a]Adjusted odds ratio only given if factor significantly associated with likelihood of consent.

(in this case over the age of 85) giving consent has been reported in other studies.[14] The year that the patient was invited to enter the study was the most important patient factor, with a patient approached in 2004 being twice as likely to take part as one approached in 2001.

There are several possible explanations as to why there was such a strong association between when a patient was recruited and whether or not they gave consent. It is possible that changes to investigator training methods had an impact on the way in which investigators conducted the consent process (Table 1). Many doctors encounter problems obtaining consent satisfactorily,[15] and changes in training may have helped to alleviate some of these. An individual patient meta-analysis published at the end of 2002[16] was incorporated into the training sessions in 2003. This helped demonstrate the uncertainty as to whether the benefits of warfarin outweighed potential harm as compared to aspirin in the study age group. Investigators trained after this date may, therefore, have been more confident that equipoise existed for individual patients,[4] possibly resulting in an increased likelihood that a patient would consent to take part. There were several changes to trial procedures (see Table 1) which might have had an effect, though most of these changes will have affected the trial 'upstream' of the consent process. These amendments potentially had a two-fold effect. Simplification of study procedures resulted in a reduced workload for investigators, minimizing the negative impact that a time-consuming protocol has on a physician's ability to engage with the research,[3] thus making the project more attractive to them.[17] Changes to both payment methods and study procedures reduced the time between investigator training and commencement of patient recruitment (from approximately 4 months to approximately 2 months) so investigators were possibly more familiar with the trial rationale and protocol than they would be after a lengthy delay. Haidich and Ioannidis[18] demonstrated in a secondary care setting that the longer the gap between study commencement and enrolment of the first patient, the less likely the site is to recruit well. The broadening of the inclusion criteria to allow people on warfarin to be considered may be a partial explanation of the temporal trend observed in patient consent, though it is not clear why there should have been a 2-year lag before it had an effect. It may be that there was a secular change in patient attitude, either to trial participation in general or value of warfarin in particular over the study period. Warfarin use has become more common in older people over time,[19] and this may have influenced willingness to participate.

Practice and practitioner factors

In this study, older physicians were more likely to obtain consent than younger physicians, although there was not a simple linear relationship with age, and a higher proportion of patients from smaller practices gave consent than from larger practices. Practitioners can be uncomfortable describing personal equipoise and the randomization process[20] and will often emphasize aspects of the trial that they expect patients to understand more easily.[21] These difficulties may be mitigated in smaller practices where continuity of care is possible, and physicians can get to know their patients better, giving patients a feeling of security[22] and the primary care physician a better understanding of[23] and increased feeling of responsibility towards their patient.[24] This enables them to be both more selective about which patients they invite, and more confident in their relationship.

The effect of age may reflect a number of factors, including variations in consulting style or differing attitudes to warfarin. Older doctors are seen to be more willing to listen and more reassuring than younger doctors, and are viewed more positively by older patients.[25]

Strengths and limitations

The patients in this analysis were all considered eligible for the study by their primary care physician and all attended a clinic appointment, so were not averse

to trial participation *per se*. Therefore, the factors considered here impact directly on the process of obtaining consent, rather than on other parts of the patient pathway leading to trial participation, such as willingness to attend, or physician decisions about eligibility. Another strength is the large size, and the high degree of data completeness, with over 90% data completeness (worst data item was prior aspirin use, with 7.8% missing data).

There are some weaknesses to this analysis. Although it demonstrates that a wide variety of factors influence recruitment, it does not allow us to understand how or why these characteristics have such a significant effect. It is based around a single trial, so may be difficult to generalize to other primary care trials. However, there are findings here that are of general interest. The effect of practice size and the impact of year of recruitment are unlikely to have been primarily related to the nature of the trial interventions. Furthermore, Donovan *et al.*[26] demonstrated that the way that study treatments are described to a patient influences whether or not they are willing to take part, so it is possible that even study-specific factors such as prior use of warfarin were influenced by how the investigator conducted the consent process.

Implications for future primary care-based RCTs

The two-fold difference in the likelihood of whether or not a patient would give consent over the time course of the study having adjusted for influence of other patient and practice factors suggests that the conduct of a trial can have a dramatic effect on patient recruitment. It is possible that changes made to investigator training, study procedures and payment methods account for this finding. As the analysis only considered patients who were eligible for the study and who went through the informed consent procedure, the changes must have affected either the type of patients attending this appointment, or what was said to them during the consent process. The evidence base for how to train investigators and conduct trials in primary care is poor.[5] This analysis suggests that research into this area could yield important benefits in terms of enhancing recruitment to future studies.

Declaration

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Ethical approval: Approval for the main trial was obtained from West Midlands Multi-Centre Research Ethics Committee in 2000 and from all appropriate Local Research Ethics Committees and Primary Care Trusts.

Conflicts of interest: No authors have any conflict of interest.

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Appendix Three: Impact of Study Design on Patient Recruitment Family Practice Publication

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Impact of study design on recruitment of patients to a primary care trial: an observational time series analysis of the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) Study

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Background. Recruitment targets to randomized controlled trials (RCTs) are often not met. Many interventions are used to improve recruitment but there is little empirical evidence on whether these approaches work.

Objective. To examine whether changes to the design and conduct of a primary care-based RCT were associated with changes in patient recruitment.

Methods. An observational time series analysis of recruitment to a primary care-based multicentre RCT of aspirin versus warfarin for stroke prevention, which involved 330 practices. Several changes to the trial protocol and procedures were made over the 4 years of patient recruitment. For each quarter throughout the recruitment period, the recruitment rate per 1000 total population in active practices was calculated.

Results. The recruitment target of 930 patients was exceeded. Fluctuations in recruitment rate occurred during the recruitment period. Following protocol changes aimed to reduce clinical workload, there was a significant increase in recruitment during the final 6 months of the study, during a period when there was not a similarly large increase in the total population available.

Conclusions. These findings suggest that the conduct of a trial is an important consideration if studies are to recruit successfully. Expanding the number of centres may not be the most effective way to improve recruitment.

Keywords. Patient recruitment, RCT, trial design.

Background

Randomized controlled trials (RCTs) are accepted as the gold standard for evaluating health care interventions.[1–3] However, recruitment to RCTs remains problematic, with many studies still struggling to achieve targets.[2,4,5]

A Cochrane review, which identified 15 studies of recruitment strategies (RCTs or quasi-randomized trials) found that these approaches had little or no impact on patient recruitment.[6] A practical guide for researchers in primary care emphasizes the importance of minimization of investigator workload, broad inclusion/exclusion criteria and simplification of protocol[7–9] While this guidance has an inherent logic to it, there is little empirical evidence that any of the recommended approaches actually work.[10]

Haidich *et al.*[11] conducted a study examining recruitment patterns to a number of human immunodeficiency virus efficacy trials. They found that the recruitment peak in almost all trials happened within the first 6 months and that recruitment in the first few months was indicative of the future pace; those centres recruiting well initially were more likely to achieve their targets. They also found that few slow starting trials managed to significantly accelerate recruitment, despite the fact that many relaxed restrictive entry criteria to boost recruitment. They concluded that initial pace of recruitment should be used to decide on the feasibility of completing an under performing trial.[11]

The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) Study[12,13] is an example of a trial where initial recruitment did not predict the overall recruitment rate. BAFTA was a primary care-based

multi-centre RCT that initially aimed to recruit 1240 patients aged ⩾75 years who had a diagnosis of atrial fibrillation (AF), to a study of aspirin versus adjusted dose warfarin for the prevention of stroke. Recruitment to the study was initially very slow. A new power calculation was carried out and a revised target (930) was set. This target was eventually achieved, in conjunction with a number of changes to the recruitment process (see Fig. 1 and Table 1).

Previous analysis of BAFTA recruitment demonstrated that patients in the final year of recruitment were almost twice as likely to participate as those in the first year.[14] This suggests that changes introduced during the course of the trial might have influenced recruitment. The aims of this paper are to describe the actions taken to improve recruitment in the BAFTA trial and to examine recruitment patterns to try to identify which of the changes made to the design and conduct of the study were most closely associated with recruitment.

Recruitment to the BAFTA trial

Each participating practice nominated one primary care physician (GP) to act as local investigator and one practice nurse to assist the GP with the identification and recruitment of patients. The research team trained all nominated practice staff in study procedures and good clinical practice. Training was carried out over the 4-year patient recruitment period (2001–04).

After attending a training session, practices were responsible for the identification of potentially eligible patients (see Fig. 2). An electrocardiogram (ECG) was carried out on all patients with an AF diagnosis in their medical records or who were found to have an irregular pulse during opportunistic screening. When AF was shown on the study ECG, GPs examined patients' medical records to establish the presence of study exclusion criteria. If the GP was in equipoise over whether to treat a patient with aspirin or warfarin, then the patient was invited to an appointment to discuss trial participation.

Actions taken to improve recruitment

Over the recruitment period, inclusion criteria were revised; procedural changes were introduced to reduce primary care workload and time to recruitment; more sites were enrolled and our approach to the recruitment and retention of practices changed (see Table 1).

Statistical analysis

To address the question: was the increase in recruitment over time due to an increase in the size of the study population or due to changes in study design and conduct, we calculated the recruitment rate per 1000 population.

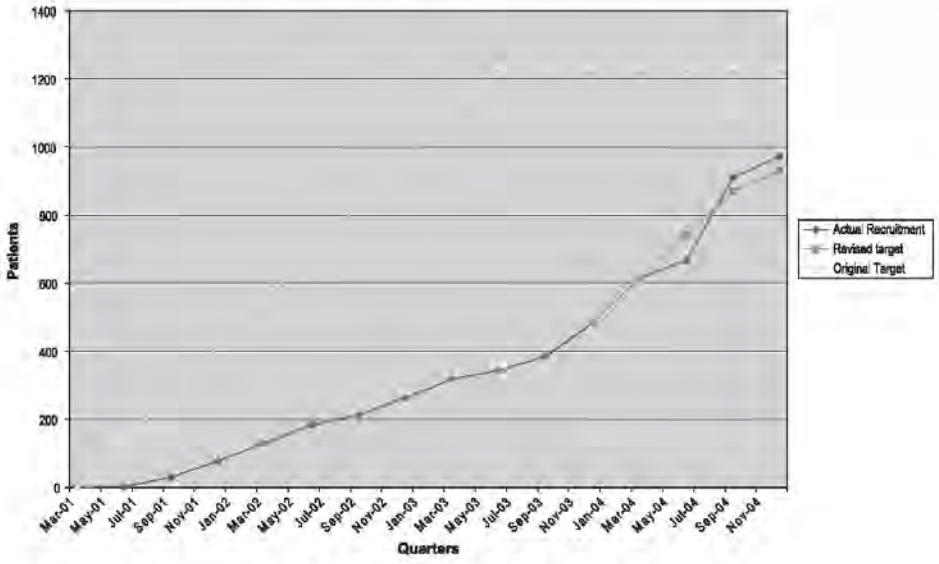

FIGURE 1 *BAFTA recruitment targets*

TABLE 1 *Changes to trial procedures*

Protocol amendments						
Change number	Date introduced	Problem	Change	Procedure prior to change	Procedure post change	Expected impact
1	2002	Lower than expected prevalence of AF on study ECG	Amendment to inclusion criteria 1 Allows patients to be potentially eligible if have ECG diagnosis of AF in records but sinus rhythm (SR) on study ECG	All patients ECG'd prior to determining eligibility and ineligible if SR on study ECG	Patients with ECG in records (within 2 years) showing AF now potentially eligible. Only patients consenting to participation have study ECG, allowing categorization into AF or paroxysmal AF	Reduction in investigator workload Increased number of potentially eligible patients
2	2002	Higher rate of patients already taking warfarin than expected from the literature	Amendment to inclusion criteria 2 Broadening of inclusion criteria to allow people on warfarin to be considered	Patients on warfarin were ineligible.	No change to procedure	Increase in numbers eligible
Procedural changes						
3	2002	Intensive practice workload	Reduced workload 1 ECGs only carried out on potentially eligible patients	ECGs carried out on all patients with AF on computer searches and patients with an irregular pulse	ECGs now only carried out on potentially eligible patients	Decreased workload
4	2003	Intensive practice workload	Reduced workload 2 Data on past medical history and medications only collected on potentially eligible patients	Data collected on all patients with AF	Practices no longer search medical records for detailed data for patients who are ineligible for the trial	Decreased workload
5	2004	Intensive practice workload	Reduced workload 3 Evidence of AF in patient records used to determine eligibility, patients only have ECG once they have consented to participation	All potentially eligible patients received a study ECG prior to randomization	Practices look for evidence of AF in the records when determining eligibility for the study. Patients then invited to participate and receive an ECG if they consent to randomization	Decreased workload
6	2004	Intensive practice workload/recruitment timeframe (recruitment closed September 2004)	Reduced workload 4 Practices no longer carried out opportunistic pulse screening	All patients without AF on computer searches would have their pulse screened to identify potential new cases of AF	Opportunistic screening no longer carried out. Incident cases of AF could still be considered	Decreased workload and shortened time to complete recruitment process
7	2004	New trial team approach to site retention		Once trained, the study team would endeavour to keep each site as participants, offering help and support where appropriate	Under performing practices or sites who were unsure about their ability to carry out the work within the required time were simply allowed to withdraw	Enthusiastic successful practices to remain active, ensure optimal recruitment and optimal allocation of study team resources

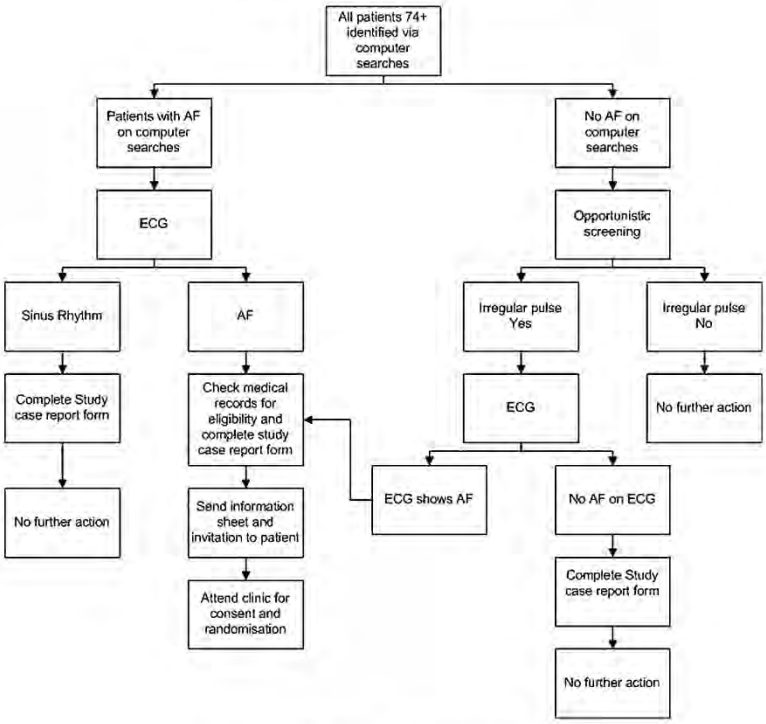

FIGURE 2 *The recruitment process to BAFTA*

The recruitment period was divided into 3-month periods. Only data from active practices (those who had reviewed their patients for eligibility or had invited two or more patients to attend a study clinic during the period) were included. For each quarter, the denominator was the population of patients aged ⩾75 years in active practices. In order to determine whether there was a significant change in recruitment rate, we conducted change point analysis with the moving F statistic using the first seven quarters as the baseline sample and a moving average of three quarters.[15]

Results

A total of 535 practices attended study training sessions, with 330 continuing through to active participation. Of those, 257 sites saw at least one patient at a randomization clinic appointment and 234 recruited one or more patients. The revised target of 930 patients was exceeded, with 973 people recruited into the trial. An average of 65 patients were recruited per quarter (range 4–219) (see Fig. 3).

Recruitment fluctuated during the recruitment period (see Fig. 3). There was a significant increase in recruitment rate ($P < 0.05$) in the last 6 months of the study (see Fig. 4).

Discussion

This study found that the increase in recruitment in the last 6 months of the study was associated with a significant rise in recruitment rate per 1000 population rather than with an increase in the size of the study population. Inclusion of more sites to increase the total study population would seem an obvious way of improving recruitment and is an approach that many trials utilize.[3,9,16] However, this analysis indicates that recruitment to BAFTA was affected more by factors influencing the proportion of eligible patients participating.

The protocol modifications in BAFTA had mixed success. Restrictive inclusion criteria can have a profound impact on recruitment and broadening of criteria is an approach often used by investigators to improve accrual.[10,11] In this study, broadening of

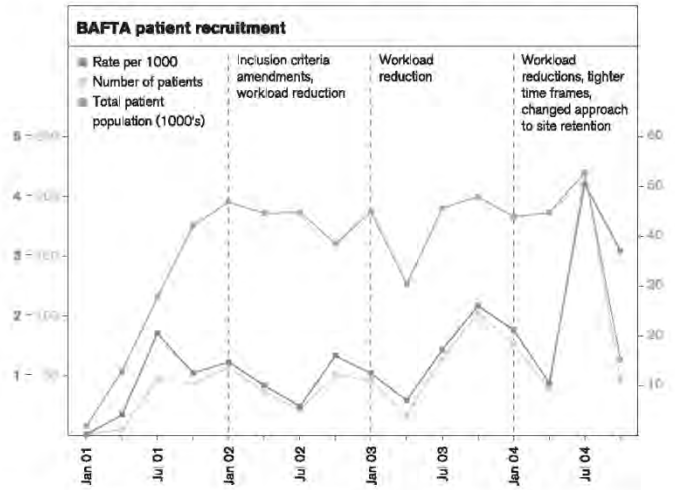

FIGURE 3 *BAFTA patient recruitment with timing of changes to the recruitment process*

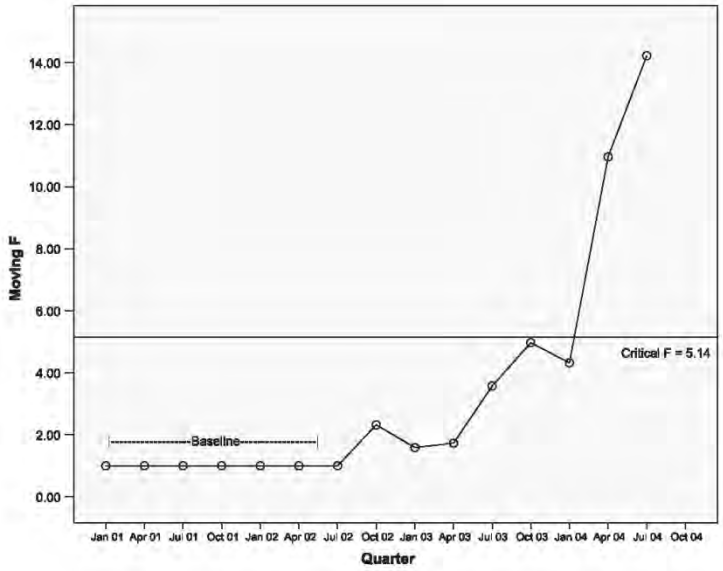

FIGURE 4 *BAFTA patient recruitment over time using the Moving F statistic*

inclusion criteria had no immediate impact on recruitment, though inclusion of patients already taking warfarin did have a longer term effect[13] (see Table 1 and Fig. 3).

A number of changes to reduce investigator workload were introduced (see Table 1 and Fig. 3). Minimization of investigator workload is often cited as an important facilitator to recruitment.[17,18] In 2002, practices were asked to carry out ECGs only on people who were potentially eligible for inclusion instead of on all patients. In 2003, data collected on patients who were ineligible for the study was reduced. In

2004, the requirement for investigators to carry out opportunistic screening to identify patients with AF was removed. These latter changes were associated with an increase in recruitment (see Fig. 3). The large recruitment increase in 2004 could have been a result of the cumulative effect of the three protocol change reductions in workload that took place over the whole recruitment period rather than as a direct result of changes that were made in 2004.

There may be other explanations for the observed increase in recruitment. In 2004, a new approach to site retention was adopted by the research team, with underperforming or overstretched practices simply withdrawing from participation (see Table 1). Remaining practices were likely to have been more interested in the study question or more able to incorporate the extra workload into practice. Furthermore, these practices had tight timeframes within which to complete recruitment so that they may have given the study a higher priority.

It is possible that factors extrinsic to the trial might have been responsible for the observed increases. In 2002, an individual patient data meta-analysis was published, which helped underline the uncertainty surrounding the benefits and harms of aspirin versus warfarin in the >75 age group.[19] This new evidence was incorporated into investigator training in 2003. This may have made GPs more confident about the treatment uncertainties and therefore more comfortable with explaining equipoise to individual patients.[14] How a study is explained to a patient has been shown to impact on their willingness to participate[20] so better acceptance of the study question by investigators may lead to more patients giving consent. The increased recruitment rates could also be as a result of changes in patient attitudes, either to warfarin or to participation in trials in general. Warfarin use in older people has increased[21] and this may account for their increased willingness to participate.

Strengths and limitations

A strength of this study is that it demonstrates identifiable time points in the recruitment period, which can be related to both protocol and procedural changes. Unfortunately, it is not possible to determine what aspects of the steps taken to improve recruitment were actually responsible for the changes in recruitment. The large jump in recruitment seen in 2004 may have been caused by any one of the interventions described or by a combination of all of them. Nevertheless, this analysis does provide evidence that it is possible to significantly improve recruitment rates without simply recruiting more centres and gives an insight into ways in which this may be achieved.

However, it is difficult to generalize from the particular (i.e. recruitment of older people to a trial of AF) to the general (i.e. recruitment to primary care trials across different diseases and ages). Nevertheless, the lessons learnt, for example, with regard to workload minimization and simplification of study protocol, could be considered by investigators designing other trials.[7,8]

Implications

The findings suggest that the conduct of a trial is a vital consideration if accrual targets are to be reached. Minimization of investigator workload is important. Care should be taken to ensure that only relevant data are collected. For example, data collection on non-eligible patients to consider generalizability issues diverts resources from patient recruitment. Expanding the number of active sites, while logical, is not necessarily the most effective way of improving recruitment. It may be more useful for trials to consider whether other approaches would be more appropriate before investing time and money in expansion. Care should also be taken when using early recruitment data to predict overall recruitment or to determine the continued feasibility of a study[11] since initial patterns may not account for the potential success of protocol changes. Therefore, one very important implication of these data is how funders of research interpret initial recruitment data. If the funder had not shown flexibility in extending the trial, BAFTA could have failed. Given the major clinical impact of the study, this would have been unfortunate. Reasonable time for protocol amendments to take effect is needed and funders need to balance reasonable desire to stop a trial where recruitment targets seem futile with the cost to society of never answering the research question. Prospective studies to test the impact of interventions on recruitment rates would benefit future RCTs.

Declaration

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Ethical approval: West Midlands Multi centre Research Ethics Committee in 2000 and from all appropriate Local Research Ethics Committees and Primary Care Trusts (MREC 99/7/57).
Conflict of interest: none.

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Appendix Four: Topic Guide

Objectives

- To identify problems, barriers and facilitators to participation in research from the GP perspective
- To understand how GPs conduct the consent process
- To explore the reasons for differences between practitioners in the proportions of eligible patients who give consent to participation

Introduction

- Introduce: self and study; expected length of interview; voluntary and can withdraw at any time; explain they have the option to not answer specific questions; confidentiality; sign consent form

Background

Practice background

- Number of GPs in the practice
- Availability of other staff (ie research nurses/receptionists/administrators)
- Is there a personal list system in operation?
- Has your practice ever taken part in any research before?
    - What kind?

Personal background

- When and where did you qualify?
- Have you any extra qualifications/training?
- How long have you been a GP?

- How long have you worked in this practice?
- Have you ever taken part in any research before?
    - What kind, capacity, enjoy?

BAFTA involvement

Can you describe the study?

- What in your view was the study question?
- What was your view/attitude/feelings towards the study question?
    - How did you feel about the study drugs involved?

Why did you decide to do the study?

- How do you feel about research in general
- What relevance did this question have?
- Why them as opposed to other GP in the practice

Patient Recruitment

Taking part in the study

- Could you describe your overall experience of taking part
    - How did you find the study procedures?
    - How did you find the study workload?
    - How useful did you find the study manual
    - Was there a time lag between training and recruiting – any impact
    - How do you feel about the reimbursement levels/methods

Study training

- Could you tell me about the initial meeting you attended about the study?
    - What did it involve?
    - Did any parts of the meeting work well? What were they?
        - If no, how do you think it could have been improved?
    - Did any parts of the meeting work not so well?
        - How do you think it could have been improved?
        - If no, was there anything that could have been done differently that would have improved it?
    - What do you think this session should have covered that wasn't included?
    - How do you feel about the session overall?
        - How prepared for taking part did you feel?
        - What affect did it have on your knowledge of the subject?
        - How do you feel about the duration of the training?
    - How would you have felt about DVD/video format training?
        - How would you have felt if you had been sent the studypaperwork instead of attending this meeting?

Specific issues regarding recruitment to BAFTA

- How did you identify patients who you thought may be eligible for the study?
    - How did the opportunistic screening work?
    - Were all practice staff involved?
    - How did you involve them?
    - How did you identify patients already having AF?
- How did you choose which patients to invite to randomisation clinic?

    - Did you invite all eligible patients or only those you know well
    - Did you exclude any specific groups?
        - Why
- Can you tell me how the consent appointment was done in your practice?
    - Who was involved in the appointment?
    - How long before this appointment did patients receive the information sheet?
- Can you tell me how you described the study to a patient?
    - How did you explain uncertainty?
        - Did you describe it as personal or community uncertainty?
- How do you feel about saying to patients 'I don't know'
    - How do you think patients would feel about you saying I don't know?
- How did you explain the need for randomisation?
    - What language did you use?
- How did you explain the randomisation process?
    - What language did you use?
- Could you tell me what you see as the need for randomisation?
- How did you describe the relative pros and cons of the study drugs?
    - Did you always describe it in the same way?
    - Did you tailor it to individuals?
        - How did you decide what to say to individuals?
- Thinking about patient follow up, how did that work?
    - How did you know when they were due to come and see you?
    - How useful were reminders?

Broad trial issues

- Can you tell me about any general feelings you have about involving patients in trials?
- What do you see as the advantages of using rct design?
- What do you see as the disadvantages?
    - Could you tell me how you feel about the ethics of RCTs?
    - Some doctors say putting patients in trials may have an influence on the doctor\patient relationship. Could you tell me how you feel about that?
    - Some doctors say they feel responsible if patients have event or are on what turns out to be inferior treatment. Could you tell me how you feel about that?
    - Some doctors feel that putting patients into trials has an effect on their clinical autonomy. Could you tell me you feel about that?
- Do you have a gut feeling about which treatment will be shown to be best?
    - What do you think results are going to be?
    - What do you hope they will be?

Further research

- Would you get involved in similar research in the future?
    - Can you explain why?

Further comments

- Do you have any other thoughts or comments about being involved in BAFTA, or about trials in general?

Appendix Five: Coding Framework Version 3

1	Risk and Responsibility	
	1.1 BAFTA	How GPs feel towards the specific study question
	1.2 Motivation	Why GP/practice took part in BAFTA
	1.3 Changes in attitude to BAFTA	Changes in attitudes throughout the duration of the study (inc outside influences)
	1.4 Risk	Risk and their patients; risk and trials (inc. Direct and indirect reference to risk)
	1.5 Ethics of Trials	How GPs feel about the ethics of RCTs; references to drugs company research
	1.6 Responsibility	GPs feelings of responsibility for their patients/for research
	1.7 Patients	How GPs feel about: putting patients on warfarin/aspirin; putting patients into trials; explanation of trials and/or trial drugs
2	GP Experience & Understanding	
	2.1 Overall experience	How GPs felt overall about taking part in BAFTA
	2.2 Practical Issues	How OS carried out; how consent clinics were run; study team; usual practice; comments on paperwork; workload; how patients chosen; remuneration
	2.3 Spin offs for the practice	Any impact on the practice as a result of the trial but not directly relevant (ie AF registers)
	2.4 Experience from other studies	Discussion of other studies they have participated in; recruitment of different patient groups
	2.5 Issues affecting recruitment and retention	Local consultants; existing treatment; recruitment of practices
	2.6 Suggestions to enhance experience	Comments on what could be done to improve experience
	2.7 Understanding of BAFTA	Understanding/misunderstanding of: the study question or protocol; trial procedures
	2.8 Understanding of trials	Understanding need for randomisation, primary care evidence etc.
	2.9 Study team	Relationship between study team and practice, ie. trust in the team; support from the team
	2.10 Training	Comments on training given to BAFTA local investigators
	2.11 Discussion of uncertainty	How they feel about discussing treatment uncertainty with their patients
	2.12 Equipoise	Understanding/comments on uncertainty concept

3	GP/Patient interaction	
	3.1 Explanation of trial to patients	How GPs explain the trial
	3.2 Description of Uncertainty	How GPs explain the uncertainty concept
	3.3 GP/Patient relationship	How trials impact on the doctor/patient relationship
	3.4 Patient experience	GP opinion about what patients think about trials
	3.5 Patient understanding	GP opinion about how well patients understand BAFTA and/or trial concepts; what information they wanted and how they wanted to be given it
	3.6 Patient attitude to study drugs	GP thoughts on what patients felt about the study drugs
	3.7 Clinical Autonomy	How GPs feel about clinical autonomy

Appendix Six: Involvement of Colleagues in the Research

I was responsible for the design and conduct of the systematic review, with input from Professor Jonathan Mant. I was also responsible for the collation and extraction of recruitment data from the BAFTA database, for the data checks and for the basic data analysis in chapters five and six. Trial statisticians Andrea Roalfe and Roger Holder were responsible for the more complex analysis that was requested by the journal at publication (the logistic regression, multi-level modelling and the moving F statistic). I was responsible for the design of the interview study, for carrying out all interviews and for all the qualitative data analysis. I carried out the transcription of four interviews, and administrative staff were responsible for transcribing the remaining interviews. I was also responsible for writing all drafts of all publications to have emerged from the thesis (See Appendices 2 and 3).

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