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# Antenatal screening for haemoglobinopathies in primary care: a cohort study and cluster randomised trial to inform a simulation model. The Screening for Haemoglobinopathies in First Trimester (SHIFT) trial

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 03/02/03. The contractual start date was in October 2004. The draft report began editorial review in August 2008 and was accepted for publication in July 2009. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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# Abstract

## Antenatal screening for haemoglobinopathies in primary care: a cohort study and cluster randomised trial to inform a simulation model. The Screening for Haemoglobinopathies in First Trimester (SHIFT) trial

E Dormandy, S Bryan, MC Gulliford, TE Roberts, AE Ades, M Calnan, K Atkin, J Karnon, PM Barton, J Logan, F Kavalier, HJ Harris, TA Johnston, EN Anionwu, V Davis, K Brown, A Juarez-Garcia, V Tsianakas and TM Marteau*

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**Objectives:** To assess the effectiveness, cost-effectiveness, acceptability and feasibility of offering universal antenatal sickle cell and thalassaemia (SCT) screening in primary care when pregnancy is first confirmed and to model the cost-effectiveness of early screening in primary care versus standard care.
**Design:** A population-based cohort study, cluster randomised trial and refinement of a published decision model.
**Setting:** Twenty-five general practices from two UK primary care trusts (PCTs) in two inner city boroughs with a high proportion of residents from minority ethnic groups.
**Participants:** Practices were considered eligible if they agreed to be randomised and they were able to provide anonymous data on all eligible pregnant women. Participants were at least 18 years old and consented to take part in the evaluation.
**Interventions:** Practices were allocated to intervention, using minimisation and stratifying for PCT and number of partners at the practice, as follows: screening in primary care with parallel father testing (test offered to mother and father simultaneously; *n* = 8 clusters, 1010 participants); screening in primary care with sequential father testing (test offered to father only if mother identified as carrier; *n* = 9 clusters, 792 participants); and screening in secondary care with sequential father testing (standard care; *n* = 8 clusters, 619 participants).
**Main outcome measures:** Data on gestational age at pregnancy confirmation and screening date were collected from trial practices for 6 months before randomisation in the cohort phase. The primary outcome measure was timing of SCT screening, measured as the proportion of women screened before 70 days' (10 weeks') gestation. Other outcomes included: offer of screening, rates of informed choice and proportion of women who knew the carrier status of their baby's father by 77 days (11 weeks).
**Results:** For 1441 eligible women in the cohort phase, the median [interquartile range (IQR)] gestational age at pregnancy confirmation was 7.6 weeks (6.0 to10.7 weeks) and 74% presented in primary care before 10 weeks. The median gestational age at screening was 15.3 weeks (IQR 12.6 to 18.0 weeks). Only 4.4% were screened before 10 weeks. The median delay between pregnancy confirmation and screening was 6.9 weeks (4.7 to 9.3 weeks). In the intervention phase, 1708 pregnancies from 25 practices were assessed for the primary outcome measure. Completed questionnaires were obtained from 464 women who met eligibility criteria for the main analysis. The proportion of women screened by 10 weeks (70 days) was 9/441 (2%) in standard care, compared with 161/677 (24%) in primary care with parallel testing, and 167/590 (28%) in primary care with sequential testing. The proportion of women offered screening by 10 weeks (70 days) was 3/90 (3%) in standard care (note offer of test ascertained for questionnaire respondents only), compared with 321/677 (47%) in primary care with parallel testing, and 281/590 (48%) in primary care with sequential testing. The proportion of women screened by 26 weeks (182 days) was similar across the three groups: 324/441 (73%) in standard care, 571/677 (84%, 0.09) in primary

care with parallel testing, and 481/590 (82%, 0.148) in primary care with sequential testing. The screening uptake of fathers was 51/677 (8%) in primary care with parallel testing, and 16/590 (3%) in primary care with sequential testing, and 13/441 (3%) in standard care. The predicted average total cost per pregnancy of offering antenatal SCT screening was estimated to be £13 in standard care, £18.50 in primary care with parallel testing, and £16.40 in primary care with sequential testing. The incremental cost-effectiveness ratio (ICER) was £23 in primary care with parallel testing and £12 in primary care with sequential testing when compared with standard care. Women offered testing in primary care were as likely to make an informed choice as those offered screening by midwives later in pregnancy, but less than one-third of women overall made an informed choice about screening.

**Conclusions:** Offering antenatal SCT screening as part of pregnancy-confirmation consultations significantly increased the proportion of women screened before 10 weeks (70 days), from 2% in standard care to between 16% and 27% in primary care, but additional resources may be required to implement this. There was no evidence to support offering fathers screening at the same time as women.

**Trial registration:** Current Controlled Trials ISRCTN00677850.

**Funding:** The National Institute for Health Research Health Technology Assessment programme.

# Contents

# List of abbreviations

| | |
|---|---|
| CEA | cost-effectiveness analysis |
| CF | cystic fibrosis |
| EDD | estimated delivery date |
| GEE | generalised estimating equation |
| GP | general practitioner |
| HCP | health-care professional |
| HTA | Health Technology Assessment |
| ICC | intraclass correlation coefficient |
| ICER | incremental cost-effectiveness ratio |
| IMD | index of multiple deprivation |
| IQR | interquartile range |
| LMP | first day of the last menstrual period |
| MCMC | Markov chain Monte Carlo |
| MRC | Medical Research Council |
| NHS | National Health Service |
| NICE | National Institute for Health and Clinical Excellence |
| NSC | National Screening Committee |
| NSF | National Service Framework |
| PCT | primary care trust |
| PND | prenatal diagnosis |
| RAA | research activity agreement |
| RISP | research information sheet for practices |
| SCT | sickle cell and thalassaemia |
| SHIFT | Screening for Haemoglobinopathies In the First Trimester |
| TOP | termination of pregnancy |
| USS | ultrasound scan |
| WHO | World Health Organization |

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

# Executive summary

## Background

Haemoglobinopathies, including sickle cell disease and thalassaemia, are inherited disorders of haemoglobin. It is estimated that 7% of the world's population are carriers for either sickle cell disease or thalassaemia. Each year, up to half a million births worldwide are affected by a clinically significant form of haemoglobinopathy. There is a significant morbidity and mortality associated with haemoglobinopathies.

In 2001, the NHS Sickle Cell and Thalassaemia (SC&T) Screening Programme was set up 'to offer timely antenatal sickle cell and thalassaemia screening to all women (and couples) to facilitate informed decision making'. The programme aims to offer screening by 10 weeks' gestation. This is to ensure that the screening process is completed by 12 weeks' gestation in order for couples to have the opportunity to consider all of their reproductive choices, including prenatal diagnosis (PND) and termination of pregnancy (TOP) early in pregnancy.

It has been reported that screening is offered too late in pregnancy to allow couples the opportunity to consider all of their reproductive options. Baseline data showed that while 75% of women confirmed their pregnancies in primary care by 10 weeks, only 4.4% were screened for sickle cell and thalassaemia (SCT) trait by 10 weeks.

## Objectives

We set out to assess the effectiveness, cost-effectiveness, acceptability and feasibility of offering universal antenatal SCT screening in primary care when pregnancy is first confirmed. We compared three ways of offering antenatal SCT screening:

1. in primary care with parallel father testing, i.e. test offered to mothers and fathers at the same time
2. in primary care with sequential father testing, i.e. test offered to mothers; test offered to father only if mother identified as a carrier
3. in secondary care with sequential father testing, i.e. test offered to mothers; test offered to father only if mother identified as carrier.

## Methods

Methods included a cluster randomised trial and refinement of a published decision model (Zeuner *et al.* 1999).

### Setting

The trial took place in two inner city boroughs, ranked amongst the most deprived in England, with high proportions of residents from minority ethnic groups. We recruited 27 general practices from two primary care trusts (PCTs) to assess three different ways of offering antenatal SCT screening.

### Eligibility

Practices were eligible for the trial if (1) they agreed to be randomised and (2) they were able to provide anonymous data on all eligible pregnant women.

Anonymous data from pregnant women were included in the trial if (1) they attended participating practices, (2) they wanted to continue their pregnancies, (3) their pregnancies were less than 19 weeks 6 days' gestation at their first visit to primary care, (4) their general practitioner (GP) had no written record of SCT status, and (5) there was a reliable estimate of gestational age based on a certain first day of last menstrual period (LMP).

Fathers of babies of eligible women in practices allocated to the group offering parallel testing in primary care were eligible to be offered screening.

All participants in the trial evaluation (questionnaire or interview) were at least 18 years old and consented to take part in the evaluation.

### Randomisation

Study practices were allocated to intervention groups after they had agreed to participate and entered the run-in data collection period. The allocations for 27 practices were determined using

minimisation; stratifying for PCT and number of partners at the practice (one or two, three or more).

### Outcome measures (including assessment of validity)

The primary outcome measure was timing of SCT screening, measured as the proportion of women screened before 70 days' (10 weeks') gestation. Timing of screening was assessed by using the gestational age at test uptake, calculated from last menstrual period at date of venesection for antenatal SCT screening. These data were collected anonymously from practices and were available for all eligible pregnancies.

Other outcomes included: offer of screening, rates of informed choice, and proportion of women who knew the carrier status of their baby's father by 77 days (11 weeks). An informed choice was defined as one based on good knowledge, and consistent with attitudes towards undergoing screening.

Analysis was based on a comparison of cluster-specific proportions adjusting for age group, parity, 'higher-risk' family origin (African, Asian and South and East European origins), partnership size, PCT and baseline screening performance. An individual level analysis using generalised estimating equations (GEEs) gave consistent findings.

### Cost-effectiveness

The economic analysis sought to predict the costs associated with the strategies and their outcomes in terms of earlier uptake of screening, and rates of downstream events such as PND and TOP. A probabilistic decision analytic model was used for the analysis, drawing on Bayesian analyses of time-to-screen data from the trial for upstream costs and process measures, and data from published sources for downstream events.

## Results

Of the 27 practices allocated, two withdrew from the study before starting intervention phase data collection.

In data collected from trial practices during a 6-month period before randomisation and intervention, including 1441 eligible women, the median [interquartile range (IQR)] gestational age at pregnancy confirmation was 7.6 weeks (6.0 to 10.7 weeks) and 74% presented in primary care before 10 weeks. The median gestational age at screening was 15.3 weeks (IQR = 12.6 to 18.0 weeks), with only 4.4% being screened before 10 weeks. The median delay between pregnancy confirmation and screening was 6.9 weeks (4.7 to 9.3 weeks)

In the intervention phase of the trial, there were 2421 pregnancies identified from 25 practices, of which 1708 were eligible to be assessed for the primary outcome measure. For questionnaire-based data, 993 women who agreed to be contacted by the research team, of whom 727 agreed to take part and 511 completed questionnaires were received. Completed questionnaires were obtained from 464 women who met eligibility criteria for the main analysis.

### Effectiveness

The proportion of women screened by 10 weeks (70 days) was 9/441 (2%) in standard care, compared with 161/677 (24%) in primary care with parallel testing, and 167/590 (28%) in primary care with sequential testing. The adjusted percentage difference from standard care (95% confidence intervals, *p*-value) was 16.5 (7.12 to 25.8, 0.002) in primary care with parallel testing, and 27.8 (14.8 to 40.7, $< 0.001$) in primary care with sequential testing. The greater effect of adjustment is explained by higher baseline screening uptake in the parallel testing group.

The proportion of women offered screening by 10 weeks (70 days) was: 3/90 (3%) in standard care, compared with 321/677 (47%) in primary care with parallel testing, and 281/590 (48%) in primary care with sequential testing. The adjusted percentage difference from standard care (95% confidence intervals, *p*-value) was 39.2 (26.0 to 52.4, $< 0.001$) in primary care with parallel testing, and 44.2 (26.6 to 61.9, $< 0.001$) in primary care with sequential testing. Note that the offer of test was ascertained from practice records for intervention groups and from questionnaire respondents only in the standard care group.

The proportion (%, *p*-value) of women screened by 26 weeks (182 days) was similar across the three groups: 324/441 (73%) in standard care, 571/677 (84%, 0.09) in primary care with parallel testing, and 481/590 (82%, 0.148) in primary care with sequential testing.

The screening uptake of fathers was 51/677 (8%) in primary care with parallel testing, and 16/590 (3%) in primary care with sequential testing, and 13/441 (3%) in standard care. The proportion (%, *p*-value) of women who knew the carrier status of the baby's father by 77 days (11 weeks) was: 0/441 (0%) in standard care, 13/677 (2%, 0.003) in primary care with parallel testing, and 3/590 (1%, 0.374) in primary care with sequential testing.

### Cost-effectiveness

The predicted average total health sector cost per pregnancy of offering antenatal SCT screening was estimated to be £13 in standard care, £18.50 in primary care with parallel testing, and £16.40 in primary care with sequential testing. The incremental cost-effectiveness ratio (ICER), i.e. the cost per additional woman screened by 70 days, was £23 in primary care with parallel testing and £12 in primary care with sequential testing when compared with standard care.

### Informed choice

Women were equally likely to make an informed choice when the test was offered in primary care as when it was offered by midwives later in pregnancy. However, less than one-third of women made an informed choice about screening, reflecting poor knowledge.

### Acceptability

Qualitative analyses based on interviews with women revealed that the offer of screening in primary care was perceived as beneficial in leading to earlier detection. They did identify, however, a need for more information, in particular about the conditions for which screening was offered and the implications of testing.

### Feasibility

Qualitative analyses based on interviews with GPs revealed positive attitudes towards offering screening as part of pregnancy-confirmation consultations, tempered by concerns about the time required to offer the test during these consultations.

## Conclusions

### Implications for practice

In areas with high prevalence, offering antenatal SCT screening as part of pregnancy-confirmation consultations in primary care increases the proportion of women screened before 10 weeks (70 days). However, it is important to note that the majority of women remain unscreened at this gestational age, raising the question of whether this is the most effective model for screening. There is no evidence to support the utility of offering screening to fathers at the same time as women are offered screening. Additional resources may be required to offer screening to women as part of pregnancy-confirmation consultations in primary care. Whether this is an efficient and fair use of resource will depend upon the values attached to early screening.

There is a need to improve existing services to reduce the delay between offer of screening and carrying out the test and to improve poor levels of knowledge about the conditions and the screening process.

### Recommendations for research

Research is needed to reduce the following key uncertainties. Note that the following recommendations are equally weighted:

- The principal value of early testing is that it provides carrier couples with the option of prenatal diagnostic testing in the early stages of pregnancy and, for those found to have an affected pregnancy, the option of a termination at an early stage of pregnancy. The evidence regarding the strength of value attached to earlier terminations is weak. It would be useful to determine the impact of gestational age at screening on uptake of prenatal diagnostic testing and reproductive decisions following the detection of affected pregnancies.
- The values attached by individuals and society to having information about SCT carrier status early in pregnancy. From this trial, it is hard to ascertain the reasons why women did not have screening. It would be useful to explore their reasons and to determine whether their decision was an informed choice.
- Low uptake of fathers could threaten feasibility of early screening. Without father testing, there is no early knowledge of couple carrier status and reproductive choices are not facilitated. Limited test uptake may be explained by high levels of social and material deprivation in the trial area or if biological fathers are not registered at the same practice as the mothers. Research needs to identify the factors limiting the uptake of testing by fathers in order to determine how they can be addressed.

- Exploring other models of care to increasing the proportion of women screened by 10 weeks' gestation. Possible mechanisms include exploring further the role of midwifery, the use of Quality Outcomes framework in primary care or increasing the role of community pharmacists.
- The results of the current study suggest that antenatal SCT carrier detection may not impact negatively on the emotional well-being of pregnant women. Longer-term follow-up on larger numbers of carrier couples is needed to estimate more precisely the extent and nature of the emotional impact on them and whether there are variations according to risk to a particular type of SCT disorder. Due to the small sample, the findings in this trial should be generalised with caution.

## Trial registration

This trial is registered as ISRCTN00677850.

# Chapter 1
# Background

## Haemoglobinopathies

Haemoglobinopathies, including sickle cell disorders and thalassaemia, are inherited disorders of haemoglobin. It is estimated that 7% of the world's population are carriers of a potentially pathological haemoglobin gene.[1] Haemoglobinopathies are among the commonest recessively inherited disorders in north-west Europe. There is a significant morbidity and mortality associated with haemoglobinopathies.

## Global context

Each year up to half a million births worldwide are affected by a clinically significant form of haemoglobinopathy.[1] Haemoglobinopathies most commonly occur in populations originating from Africa, Asia and the Mediterranean. Due to patterns of migration, they are also seen in parts of the world such as the Caribbean, UK, Northern Europe and North America.[2]

In 2006, the Secretariat of the World Health Organization (WHO) acknowledged the global burden of haemoglobinopathies, expressed concern that they were 'not officially recognised as priorities in public health', and 'deplored the inequality of access to safe and appropriate genetic services'.[3] In response to this report, the 59th World Health Assembly urged member states to implement comprehensive programmes for the prevention and management of sickle cell anaemia.[4]

Across the world, different screening strategies have been implemented. In Iran, for example, a preconceptual screening programme was introduced in 1996, followed by an antenatal programme in 2001;[5] in Belgium and France, neonatal screening for sickle cell disease is offered,[6] and in the Netherlands a pilot study of antenatal sickle cell and thalassaemia (SCT) screening has recently been completed.[7]

## Sickle cell and thalassaemia in the UK

Sickle cell disorders are estimated to affect more than 12,500 people in the UK, with approximately 240,000 healthy carriers.[8] The highest prevalence is among people of Caribbean and African ancestry. Beta thalassaemia is thought to affect more than 700 people, with approximately 214,000 healthy carriers.[8] The highest prevalence is among people of Eastern Mediterranean and Asian origin.

## Screening policy in the UK

The NHS Sickle Cell and Thalassaemia Screening Programme (NHS SC&T Screening Programme) was set up in 2001, providing the world's first linked antenatal and neonatal screening service. The overall aim of the programme is 'to offer timely antenatal sickle cell and thalassaemia screening to all women (and couples) to facilitate informed decision making'.[8] The programme provides universal antenatal screening in high-prevalence areas (prevalence greater than 1.5/10,000 births) and selective screening in low-prevalence areas.[8–10] The programme aims to offer screening by 10 weeks' gestation, to enable screening, prenatal diagnosis (PND) and any subsequent action to be completed by 12 weeks' gestation. This is in line with current National Institute for Health and Clinical Excellence (NICE)[11] and National Service Framework (NSF) guidelines.[12] NICE guidance explicitly states there should be two appointments, early in pregnancy, to ensure that women have the opportunity to make informed choices about pregnancy.

Currently, screening is offered to pregnant women in a variety of settings. The location of such appointments varies across the country: they may take place in hospital, in the woman's home or in a community-based clinic. Use of a community-based clinic (which we have designated

'community-based secondary care') appears to form the most common pattern of screening in the UK, especially in Greater London, where about half of the UK minority ethnic population live.[13] We have therefore used this pattern of screening as the comparison against which screening in general practice will be judged.

## The problem

Many at-risk pregnant women, and the fathers of their baby, are offered SCT carrier tests too late or the process of screening and diagnostic testing is taking too long to allow couples the full range of reproductive options. Reproductive options, such as prenatal diagnostic testing for carrier couples, and, when an affected pregnancy is identified, the offer of a termination, may be curtailed by the passage of time. Given the recent statutory requirements to reduce disparities between ethnic and social groups in the provision of health care,[14] it is germane to consider how antenatal screening for SCT can be organised to minimise the failure to offer screening early in pregnancy, the basic premise upon which the policy of universal screening is based.[9]

The variation in uptake of prenatal diagnostic tests is associated with the gestational age in pregnancy that the screening test is offered. For example, 73% of British Pakistani women accepted PND for thalassaemia when it was offered in the first trimester compared with 39% when offered in the second trimester.[15] This may be a particular problem for women whose pregnancies are at risk for sickle cell disease, with one retrospective study reporting that the mean gestation at which women who were carriers for sickle cell were first seen for counselling was 15 weeks, compared to 12.3 weeks for women who were carriers for thalassaemia.[16]

There are several reasons why delays occur in couples learning about their carrier status. Some laboratories produce screening test results within 48 hours,[17] whereas others take 5 days or more.[13] In addition, once results are known, it can take anything from 6 to 34 days for women to receive an appointment for counselling about diagnostic testing options.[18] Thus the speed at which laboratories process samples and report screening results can limit couples' opportunities to make informed choices.

The NHS SC&T Screening Programme has set standards for the time taken for laboratories to report a result (3 working days) and for the time interval between informing women of their carrier status and offering an appointment for a consultation to discuss diagnostic testing options (5 working days).

## Reducing delays in the screening process: the proposed trial

We propose to assess two ways of delivering antenatal screening for sickle cell and thalassaemia that have the potential to reduce delays in the screening process: offering screening at the time when women first report their pregnancies in primary care, and offering testing to the baby's father at the same time as pregnant women are offering screening.

### Time in pregnancy when screening is offered

Antenatal care is most often initiated when a woman reports her pregnancy to her general practitioner (GP), who refers the pregnant woman to a community midwife to 'book' her for antenatal and maternity care. Screening for many conditions (HIV, rubella, etc.) is usually offered at this midwifery booking appointment, which commonly occurs between 2 and 4 weeks later, with some women not having this until 15 weeks' gestation.[19] Part of the rationale for this delay is that about one in nine pregnancies spontaneously miscarry in the first trimester and it is therefore inefficient to start pregnancy care before the second trimester.[20]

The delay between reporting a pregnancy and seeing a midwife can be greater for women from ethnic minorities. It has been reported that GPs tend to book South-Asian women later than other women, despite these women reporting their pregnancies at similar gestations to other women.[21,22] The extent and possible causes of these delays are not known.

Offering antenatal SCT screening when women first report their pregnancy to their GPs has the potential to reduce this delay, a solution recognised in the recent NICE guidelines on maternity care[23] and NSF on Maternal and Child Health.[24] Such an approach to offering carrier testing in primary care for another recessively inherited condition, cystic fibrosis (CF), was successfully conducted in Manchester.[25]

The extent to which this approach is feasible, acceptable and effective in the different cultural context of sickle cell disease and thalassaemia is unknown. While offering screening at the earliest opportunity, *i.e.* as women report their pregnancies, has high face validity as a way of ensuring a timely offer and uptake of screening, it may be less effective at achieving informed choice than an offer made by a midwife as part of a longer booking appointment.

Screening by 10 weeks' gestation (70 days) maximizes the chances that the screening process is completed by 12 weeks' gestation in order for couples to have the opportunity to consider all of their reproductive choices, for example PND, which usually takes place between 10 and 13 weeks' gestation. This time frame has been guided by the NHS SC&T screening programme, NICE and NSF guidelines, and the Department of Health Operating Framework, which recommend the completion of antenatal assessments by the end of the 12th week.

Test uptake *per se* is not a desirable outcome of the offer of screening: uptake in the absence of informed choice is, in the view of the *Human Genetics Commission* and similar other bodies, an undesirable outcome. The time of offer of screening is an indirect measure of choice, based on the assumption that earlier testing provides prospective parents with more options, which may include termination. It also allows time for reflection and less pressurised decision-making.

The trial addressed the two main problems identified in two recent pilot studies offering antenatal screening for SCT in primary care.[17,26]

The first problem concerned low levels of knowledge in couples.[17] The authors of the pilot studies called for better information for those offered screening, and training of health-care professionals (HCPs). In the trial, all of those offered screening were given nationally produced information leaflets on the conditions and the screening process. All of the HCPs in the trial received training in collaboration with the Communication Skills Unit, King's College London School of Medicine, and local SCT centres.

The second main problem concerned the failure to provide primary care practices with the resources needed to provide the screening service.[26] Participating practices received NHS costs to cover the offer of SCT screening according to the study protocol, research costs for providing anonymous data on the number of pregnancies, gestational age of offer and uptake of testing, and costs to provide locum cover when GPs were trained in offering antenatal SCT screening and in the study protocol.

## Stage in the screening process when fathers are offered screening

Even if women are offered screening early in pregnancy, much time may elapse in offering testing to the baby's father, which delays couples knowing their joint carrier status. Sequential testing is the usual pattern of care offered in SCT testing. In one study, male partners were offered screening up to 4 weeks after their female carrier partners.[19] In CF screening, father testing has been conducted in one of two ways: parallel father testing, in which samples are taken and tested from both parents at the same time; and sequential testing, in which blood is taken from the father only after the woman has been tested and found to be a carrier.[27]

While parallel father testing has the potential to provide couples with information on their carrier status earlier than sequential testing, it is not known how feasible, acceptable or effective it is in the population at highest risk of SCT. The trial is based in deprived inner city areas, where the population is characterised by high mobility, low income and low educational attainment. There may be problems if few women attend with their baby's father, and there may be bureaucratic difficulties if fathers are not registered with the same GP or are not resident in the UK.[28] Estimates of partners attending for sickle cell testing after women have been identified as carriers vary between 63% and 81%.[9,16] Many issues pose problems for sequential, as well as parallel, father testing, including the suspicion and fear of stigmatisation that some men feel regarding carrier testing.[29]

To ascertain whether parallel father testing is a viable model, we evaluated how feasible, acceptable and effective it was in bringing forward the gestational age at which couples who want screening can know their joint carrier status. We evaluated this method of offering father testing in primary care only, as this is the most likely pattern of care to result in couples knowing their carrier status at an earlier gestational age than is achieved by current standard care.

## Cost-effectiveness

If the use of early testing in primary care is shown to be associated with improvements in the screening process (e.g. increases in the proportion of pregnant women undergoing screening by 10 weeks' gestation) compared with those offered screening in community-based secondary care, then it is likely that there will be cost implications for both the health-care sector and for the screened women. For example, given that one in nine pregnancies spontaneously miscarry in the first trimester,[20] some women who will undergo early testing in the primary care arm of the trial would not have been screened if the testing were delayed until the booking. In addition, parallel testing of fathers in primary care compared with the sequential testing of fathers, if accepted, will have cost implications. Again this is because of the increased risk of miscarriage in the first trimester and because the father is being tested before the results of the woman's test is known, and it is likely that the woman may not be a carrier. Therefore, the economic evaluation will take a broad perspective and consider costs falling both on the NHS and on patients.

## Future patterns of care

It is likely that as the NHS SC&T Screening Programme becomes established and the community becomes familiar with it, so the ways in which screening will be conducted will change. For example, carrier testing may take place before pregnancy, possibly linked with contraceptive advice. There will, however, always be a need to run several models of care, of which the early offer of screening in pregnancy will be an important one.[30] It is unclear whether this is best conducted by a GP, a practice nurse or a midwife. Discussions with members of primary care teams suggest that, given the way care is currently organised, the pattern we propose is the most feasible way of delivering an early offer of screening.

## Aims and objectives

The trial aims to determine the viability of offering screening in primary care when women first report their pregnancy to their GP.

## Objectives of SHIFT trial

- To assess and compare the effectiveness, acceptability and feasibility of offering antenatal SCT screening:
  - In primary care with parallel father testing, i.e. test offered to mothers and fathers at the same time.
  - In primary care with sequential father testing, i.e. test offered to mothers. The test is offered to father only if mother identified as carrier.
  - In secondary care with sequential father testing, i.e. test offered to mothers. The test is offered to father only if mother identified as carrier.
- To model the cost-effectiveness of the three patterns of care.

## Outline of the monograph

Chapter 2 presents the population-based data that were used to estimate a trial baseline regarding the delay between pregnancy confirmation in primary care and time of antenatal SCT screening. Chapter 3 describes the training programme developed to enable HCPs to integrate the offer of SCT screening into pregnancy confirmation visits in primary care as required by the interventions that formed part of the SHIFT Trial.

The trial design and results are presented in Chapter 4 (clinical effectiveness), Chapter 5 (cost-effectiveness and modelling), Chapter 6 (informed choice), Chapter 7 (acceptability to women) and Chapter 8 (feasibility in primary care). Chapter 9 summarises the main findings of the trial and makes recommendations for future policy, practice and research.

# Chapter 2

# Estimating the delay between pregnancy confirmation and screening: a population-based cohort study

## Introduction

Using population-based data obtained prior to the intervention phase of the trial, we report the delay between pregnancy confirmation in primary care and time of antenatal SCT screening, and examine the extent to which patient and practice characteristics are associated with the delays. The data reported in this chapter are published.[31]

## Method

A cohort study was conducted of all pregnancies reported in 25 general practices from two primary care trusts (PCTs).

### Eligibility

Practices were eligible for the trial if (1) they agreed to be randomised and (2) they were able to provide anonymised data on all eligible pregnant women.

### Recruitment

All general practices in two PCTs (123 general practices) were sent a written invitation to take part in a trial examining the feasibility, effectiveness and acceptability of offering antenatal SCT screening in primary care. The methods used to recruit and retain practices is described in Appendix 1. Thirty-two practices expressed an interest in taking part and 27 agreed to participate in the trial. Two practices subsequently withdrew.

### Setting

The two PCTs are ranked among the most deprived in England (sixth and 13th out of 354 boroughs) and about 40% of the population is from minority ethnic groups. The list sizes of participating practices ranged from 1300 to 15,000. The participating practices did not differ from the other practices in the two PCTs with respect to the proportion of single-handed GPs ($p = 0.33$); the list size per GP ($p = 0.99$); the Townsend score ($p = 0.69$) or the resident percentage of minority ethnic groups ($p = 0.80$). A universal screening policy was operating during the data collection period; that is, antenatal SCT screening was offered to all pregnant women regardless of the couples' ethnicity or family origin.[32]

### Data collection

Data were collected during 2005 to 2006 at each practice for a minimum of 6 months, with the intention of providing data on at least 33 pregnancies. If necessary, the data collection period was extended until data was available on 33 pregnancies. We report here on data collected from the 25 participating practices.

## Procedure

Anonymised data were collected for the first day of the last menstrual period (LMP), the date of the pregnancy confirmation visit in primary care and the date of the test, as defined by the date of venesection. These were used to calculate (1) gestational age at time of pregnancy confirmation in primary care and (2) gestational age at time of SCT screening. Screening was ascertained up to 26 weeks' gestation. Women who were not tested by 26 weeks' gestation were classified as not tested for the purpose of prenatal screening of the fetus.

Routinely collected data for date of birth, parity, ethnicity, previously determined SCT carrier status, date of antenatal SCT screening, and termination of pregnancy or miscarriage were also extracted from primary care computer systems. The number of pregnancies reported at each practice was checked by comparing with the number of maternity referrals made by each practice. Date of antenatal SCT screening was obtained from maternity units and laboratories at hospitals if not available through primary care.

Data for times were skewed and are reported as medians [interquartile ranges (IQRs)]. The distribution for the median delay for each participating general practice was evaluated. A multiple linear regression model was implemented, with delay between pregnancy confirmation visit and screening for each patient as the dependent variable. Explanatory variables were maternal age (continuous), parity (primiparous, multiparous and 'not known'), and ethnicity (North European, South European, African and African Caribbean, South Asian, other and mixed and not known). Our approach was informed broadly by census categories to enable comparison with previous studies. For analysis, women classified as: South European, African and African Caribbean, South Asian, other or mixed ethnicity were grouped as 'higher risk'. A random effects model, with maximum likelihood estimation, fitted using the 'xtreg' command in STATA version 9, was used to allow for clustering by practice.[33]

## Results

There were 2062 pregnancies from 25 practices that completed the run-in data collection phase.

Cases excluded from analysis:

- date of LMP unknown ($n = 62$)
- SCT carrier status already known, i.e. recorded in practice records prior to current pregnancy ($n = 299$)
- termination of pregnancy for reasons other than fetal abnormality ($n = 157$)
- miscarriage ($n = 117$)
- pregnancy confirmed after 26 weeks ($n = 126$).

There were 1441 eligible women who intended to proceed with their pregnancies. The women's median (IQR) age at LMP was 28.5 (24.0 to 33.5), and 767 (53%) were primiparous. Routinely recorded data for ethnicity were available for 837 (58%) women, with 645 (45%) from 'higher-risk' groups, including 'African Caribbean and Black African' (228), 'South European and Other European' (99), 'South and South East Asian' (260), 'Other ethnicity' (47) and 'Mixed ethnicity' (11).

From the 1441 pregnancies eligible for analysis, there were 965 (67%) women who had SCT screening tests performed before 26 weeks' gestation. The proportion screened did not vary by ethnicity. The median (IQR) gestational age at the pregnancy confirmation visit in primary care for all women was 7.6 weeks (6.0 to 10.1 weeks). The gestational age at the pregnancy confirmation visit for women who were screened by 26 weeks was 7.4 (5.9 to 9.9) weeks.

Among women with reported ethnicity available, there was a weak association between ethnicity and gestational age at booking after adjusting for maternal age, parity and clustering ($p = 0.023$). The median gestational age at booking ranged from 7.1 weeks in 'Northern Europeans' to 8.4 weeks in 'African Caribbean and Black African' groups.

Of the 965 women who underwent SCT screening, the gestational age at screening was 15.3 weeks (IQR 12.6 to 18.0 weeks), with 4.4% being screened by 10 weeks (*Figure 1*). The median delay between pregnancy confirmation in primary care and antenatal SCT screening in these women was 6.9 weeks (4.7 to 9.3 weeks).

Variation between practices was greater than expected by chance ($p < 0.001$). At the practice with the shortest delays, the median time from pregnancy confirmation in primary care to screening was 3.7 weeks; at the practice with the highest delay, the median time from pregnancy confirmation in primary care to screening was 10.0 weeks.

After allowing for practice level variation, there was no association between delay times and the measured individual patient characteristics, including maternal age, parity and ethnic group. Specifically, ethnicity was not associated with delay times, and variation between practices was not accounted for by adjusting for ethnicity. In addition, there was no association between ethnicity and gestational age at screening ($p = 0.351$) or with the proportion screened by 26 weeks ($p = 0.060$).

## Discussion

These population-based data show a 7-week delay between pregnancy confirmation in primary care and antenatal SCT screening. This delay undermines the policy and practice of facilitating informed reproductive choices early in pregnancy. These data are supported by a small retrospective study of women at risk of a sickle cell disorder that showed that some women did not have screening until 15 weeks' gestation, many weeks after reporting their pregnancies in primary care.[19] Furthermore, one-third of women across all ethnic groups reported their pregnancies to their

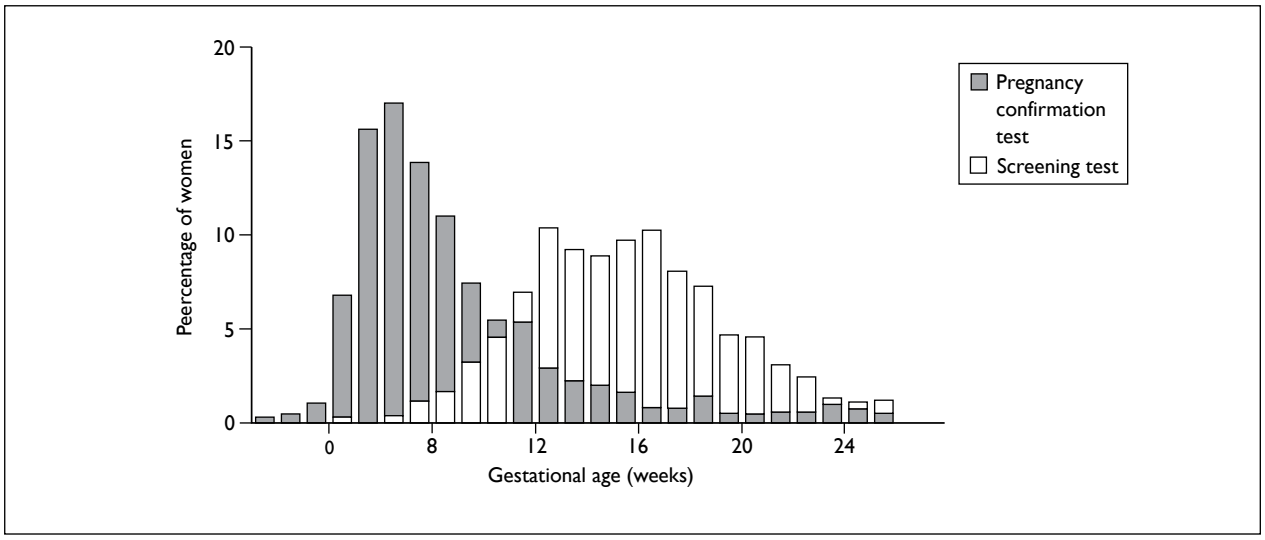


***FIGURE 1*** *Distributions for gestational age at first pregnancy confirmation visit and sickle cell and thalassaemia screening for women whose pregnancies were confirmed and screened before 26 weeks' gestation.*

GPs early in pregnancy but did not undergo SCT screening before 26 weeks' gestation. The data collected do not indicate whether this represents a service failure or individual choice not to undergo screening.

Even in this deprived inner city setting, women generally attended their general practices early in pregnancy for confirmation. The delay before screening uptake was not associated with individual women's age, parity or ethnicity. There was, however, considerable variation in the extent of delays between general practices, with the best performing practices having a median delay of just over 3 weeks from pregnancy confirmation in primary care to screening. Practice level variation may result from delays in primary care referring women for antenatal care or delays in secondary care acting on these referrals. Individual patient factors did not appear to be associated with delays in screening uptake. The results suggest there is considerable scope for facilitating timely screening through improved organisation and delivery of antenatal care.

## Comparison with existing literature

It has been suggested that the delay between pregnancy confirmation in primary care and the first midwifery appointment is greater for women from minority ethnic groups than for other women.[21,22,34] While there was some evidence that women from some minority ethnic groups attend primary care to confirm their pregnancies about 1 week later than other women, there was no evidence that the 7-week delay between pregnancy confirmation and testing was associated with ethnicity, indicating that delays within the health service, rather than women reporting late to confirm their pregnancies, are responsible for the large observed delay in testing.

## Strengths and limitations

This is the first study to examine the delay between pregnancy confirmation in primary care and antenatal SCT screening using population-based data. Limitations of the data include:

- General practices observed were not randomly selected from the 123 general practices in the two PCTs studied and therefore may not be representative of the practices in these PCTs. The variables on which we have data show participating practices were similar in practice size, deprivation and ethnicity to other practices in the study PCTs.
- Study PCTs were chosen to represent geographical areas with a high prevalence of SCT disorders and may not be representative of other areas. They represent deprived inner city areas where general practice lists are longer but primary care services are generally less well organised than those in suburban or rural areas.[35]
- Ethnicity data were not collected systematically across the practices and were available for

about half of the women. This reflects a shortfall in the collecting of basic demographic data in primary care.

- Accuracy of the collected data was dependent on the reliability and validity of the data held in GP record systems. Following fidelity checks on the number of pregnancies, we are confident that the data presented here are an accurate representation of the number of pregnancies. The reliability of data collected about these pregnancies is not known.

## Conclusion

The considerable delay between pregnancy confirmation in primary care and antenatal SCT screening may deprive couples of opportunities to opt for PND early in pregnancy. There is a need to evaluate models of care to reduce delays. The following chapter describes the development and evaluation of brief training for HCPs in primary care, in preparation for the trial aimed at evaluating primary-care-based models to reduce the delay observed in these population cohort data.

# Chapter 3

# Evaluation of brief communication skills training

This chapter describes the evaluation of communication skills training developed to enable HCPs to integrate the offer of SCT screening into pregnancy confirming consultations in primary care.

## Introduction

Communication skills training is needed to help primary care HCPs integrate the offer of antenatal SCT screening into their pregnancy-confirmation consultations. Effective training requires HCP attendance, and acquiring the necessary knowledge, skills and attitudes. Offering training on-site increases the convenience of training for participants. Providing payments to practices to reimburse them for locum cover costs incurred should also maximise attendance. Additionally, putting measures in place for training to be disseminated to non-attenders could increase the reach of the training.

There is evidence that active trainee involvement and the use of simulated patients are effective methods for developing clinical communication skills. Furthermore, using simulated patients that behave in a repeated and standardised way (standardised patients) is an effective method of training.

The assessed outcomes are based on Cervano's evaluation framework for continuing professional education. The framework includes the following dimensions:

- programme design and implementation
- learner participation (i.e. attendance)
- learner satisfaction (i.e. perceived usefulness of training)
- learner knowledge, skills and attitudes (i.e. self reported comfort and confidence with offer of screening)
- application of learning after the programme (i.e. offer of screening)
- impact of application of learning (i.e. test uptake and gestational age at test uptake).

## Methods

### Training programme

Health-care professionals confirming pregnancies in the practices randomised to primary care parallel and primary care sequential ($n = 17$) received training to enable them to present antenatal SCT screening and to facilitate informed choice. HCPs attended one of 17 training sessions, which took place within the general practices at pre-arranged convenient times. Payment for locums was provided to cover clinical time lost. Training sessions were led by the SHIFT Trial Manager and the Head of the Communications Skills Unit for Guy's, Kings and St Thomas' School of Medicine. Two weeks prior to the training session, HCPs received preparatory reading by post.

### Structure of training session

1. Trial information – 40 minutes.
2. Clinical scenario practice with simulated patients – 95 minutes.
3. General questions opportunity with a local Sickle Cell counsellor – 30 minutes.
4. Review – 15 minutes.

A clinical scenario was devised to represent a standard 'confirmation of pregnancy' appointment that would take place in general practice, and clinicians were encouraged to allocate the standard time frame for their practice of the consultation. The simulated patients were given a detailed brief, including a relevant personal, social and medical history. Once the pregnancy was confirmed the clinician was required to incorporate offering antenatal screening for SCT using the SHIFT proforma (*Box 1*) into the consultation. This required a number of prescribed key points.

***BOX 1*** *Key points to be communicated when informing women about the screening test*

- The test is optional
- What the test screens for
- What the test results mean
- Further tests
- Options if the baby is found to be affected
- How to have the first test
- How to get the results

The scenario-based skills practice included feedback from the group, the session facilitators and the simulated patients.

## Evaluation

These outcomes cover both skills and practice, and were assessed as described below.

## Skills

A short, self-administered questionnaire was developed for HCPs to self report their pre- and post-training assessments of:

- confidence in offering antenatal SCT screening
- confidence in knowledge about antenatal SCT screening
- confidence in facilitating informed choice about antenatal SCT screening
- perceived usefulness of practical skills exercises.

The selection of these items was informed by Miller's 1990[36] assertion that the evaluation of communication skills training should focus on the impact on learner knowledge, competence, performance and outcomes.

Items were scored on seven-point scales with end point 'not at all …' and 'extremely …'. Questionnaire data were maintained and analysed using SPSS.

## Analysis

Differences in mean scores were assessed using *t* tests.

## Practice

- Data on offer of screening to women in pregnancy-confirmation consultations were extracted from practice computer records.
- Data on test uptake and gestational age at test uptake were extracted from practice and laboratory records.

In addition, 6 months after training, informal face-to-face interviews were conducted with 27 HCPs (25 of whom had attended training, two of whom had not) to explore the impact of the sessions on their consultations. Interviews lasted approximately 30 minutes and were held in a private room at the HCP's general practice. All participants agreed to be audio-recorded.

# Results

## Learner participation

In total, 126 HCPs (87 GPs, 39 practice nurses) from the 17 practices were invited to attend a training session and 62% (78/126: 53 GPs, 25 practice nurses) attended. Those who joined the practices after the start of the trial ($n = 49$; 44 GPs, five nurses) were offered a training session but this did not involve simulated patients (*Figure 2*).

## Learner satisfaction, and learner knowledge, skills and attitudes

Overall, 78% (61/78) of attendees completed both pre- and post-training evaluations. After training, HCPs reported (*Table 1*):

- greater perceived usefulness of skills training when applied in practice
- greater comfort in offering screening
- greater confidence in offering screening
- greater confidence in screening knowledge
- greater confidence in the ability to facilitate informed choices.

## Application of learning after programme (i.e. offer of antenatal SCT screening)

Women consulting trained HCPs were offered antenatal SCT screening more frequently than those consulting HCPs who did not attend training ($\chi^2 = 122$, $p < 0.001$; *Table 2*). There were two types of failure to attend training: (1) HCPs in post at the start of the trial ($n = 28$) or (2) HCPs not in post at the start of the trial or locums ($n = 48$; 43 GPs, five nurses).

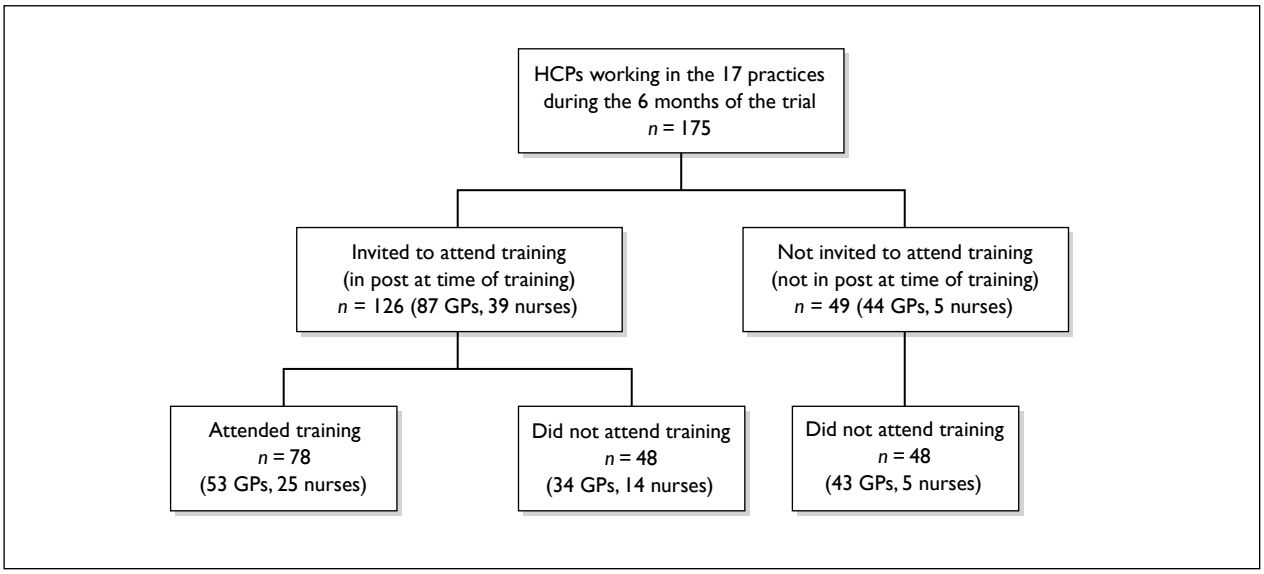


***FIGURE 2*** *Flow of health-care professionals through the training process.*

***TABLE 1*** *Pre- and post-training ratings of HCPs attending training at the start of the trial (n = 61)*

| Item | Pre-training score (mean, SD) | Post-training score (mean, SD) | Significance |
|---|---|---|---|
| **Comfort in offering test**<br>Range 1–7, 7 indicating most comfort | 4.8 (1.8) | 5.4 (1.2) | 0.05 |
| **Confident in offering the test**<br>Range 1–7, 7 indicating most confidence | 4.6 (1.7) | 5.6 (1.1) | < 0.001 |
| **Confident in knowledge about screening**<br>Range 1–7, 7 indicating most confidence | 4.3 (1.6) | 5.6 (1.1) | < 0.001 |
| **Confident in facilitating informed choice**<br>Range 1–7, 7 indicating most confidence | 4.5 (1.7) | 5.5 (1.1) | < 0.001 |
| **Usefulness of skills practice**<br>Range 1–7, 7 indicating most useful | 4.3 (1.8) | 5.6 (1.5) | < 0.001 |

***TABLE 2*** *Training attendance and clinical outcomes in the HCPs who conducted pregnancy-confirmation consultations during the trial period*

| | In post at start of trial (*n* = 92) | | In post after start of trial (*n* = 49) |
|---|---|---|---|
| | **Trained (*n* = 64)** | **Not trained (*n* = 28)** | **Not trained (*n* = 48)** |
| Mean percentage of women offered the test | 76% (642/846) | 44% (66/148) | 44% (119/269)<br>$\chi^2 = 122$, $p < 0.001$ |
| Mean gestational age at test offer (days) (SD) | 91.5<br>(35.9) | 98.5<br>(35.6) | 101.8<br>37.2<br>$F = 8.49$, df 1069, 2, $p = 0.001$ |

### Impact of application of learning (i.e. gestational age at test uptake)

Women who consulted trained HCPs were tested earlier than those who consulted untrained HCPs ($F = 8.49$, $p = 0.001$) (*Table 2*). As described above, there were two groups of HCPs who did not attend training: those in post at the start of the trial and those coming into post after the start of the trial.

### Experience of training

Qualitative analysis of interviews identified three major themes that HCPs felt were important: the effect of training on practice, the perceived benefits of training, and the challenges of training (*Box 2*).

## Discussion

Despite efforts to maximise attendance (including provision of on-site training, the timing of training sessions being negotiated with practice staff, payments for locum cover, experts in the field leading the sessions), only 62% (78/126) of invited HCPs attended. Self-reported reasons for non-attendance included holiday, sickness, and joining the practice after the start of the trial. However, for some lack of attendance could reflect lack of motivation, low prioritisation or negative attitudes towards screening. The observed rate of attendance suggests the need for the continuous offer and availability of training to provide opportunities for non-attenders who are motivated but were unable to attend initial training. Ascertaining reasons for non-attendance more systematically would allow training to be tailored to overcome these barriers. In addition, there were 49 HCPs, not in post at the start of the trial, who were involved in pregnancy-confirmation consultations. While updates and reminders were sent to practices for new joiners and locums, the majority of this group did not take part in a training session with a simulated patient. Thought needs to be given to training of a mobile group.

Health-care professionals' self-assessment of the usefulness of training, their confidence, knowledge and skill all increased with training. Given the study design, caution is needed in attributing these changes to the training per se, and in assuming that self-reported skills and knowledge strongly

***BOX 2*** *Experience of training*

**Effect of training on practice**

'It [the training] was one of the major influences on how I conducted my consultations.' (GP – HCP012)

'… It [the training] gave me a lot more confidence in talking about the test and offering it.' (GP – HCP020)

'… I don't know, it just got you thinking and I think this whole thing about screening because I used to talk about these things but it was very sort of, you know, not hit and miss but it didn't have a structure to it. I think this [the training] sort of got structure …' (GP – HCP015)

**Perceived benefits of training**

'It [the training] was very useful, very concise, told us what we need to know and what we need to do and how to do it … Because it [offering screening in primary care] was very new to us, isn't it, I mean, because we think about sickle cell thalassaemia in a different context, not in an antenatal context …' (GP – HCP09)

'Just thinking about how you might approach the situation, seeing how other people would do it, I think that's the most interesting – you already know what you might do but to see how other people manage the same situation is interesting and you learn from that.' (GP – HCP028)

**Challenges of training**

'It could have been shortened, it really only needed to target one member of our team I think. I think there was an insistence that there was quite a few of us there and it needn't have been that many people there ... It's much quicker, if you feed through to one person who's the lead in a certain area and then they can disseminate throughout the practice.' (GP – HCP08)

'It [the training session] probably could be shorter and I think that was perhaps one of the frustrations from the GPs in that we could have perhaps have done it over a lunch time. Maybe if we didn't have things like the role play, even though it could be an additional use because trying to get the message through, I would say that they [the session facilitators] probably could have condensed it.' (nurse – HCP014)

predict actual skills and knowledge. Screening was, however, offered more frequently by trained HCPs, suggesting that training had been effective in initiating the offer of screening. In addition, women who consulted a trained HCP were offered screened earlier than women consulting HCPs who were untrained and either in post at the time of training or who joined the practice subsequently.

Those attending for training may have differed from those who were invited but did not attend, in being more motivated to offer screening and this, not training, may have accounted for their greater likelihood of offering screening and the earlier gestational age at which women were screened. Evidence to suggest that training was at least in part responsible for this outcome comes from the observation that those who did not attend because they were not in post at the time of training behaved similarly to those who did not attend training, despite being in post at the time training was offered.

Training was identified as a major influence on the consultation and the opportunity to practice skills was found to be valuable. Perhaps not surprisingly, the time required for training was identified as a problem.

## Strengths and limitations

The strength of this study was the use of mixed methods to evaluate training, in particular the objective measure of the clinical impact of training, i.e. the offer of screening and the gestational age of women at screening. The main limitation was the use of an observational before and after design, limiting our ability to attribute changes to the training.

## Implications for future research or clinical practice

Using brief communication skills training to facilitate HCPs' integration of the offer of antenatal screening into their pregnancy-confirming consultations is feasible and may be effective. Although active learning methods were perceived to be useful, it is important to bear in mind that individuals may have different learning style preferences. Further work investigating factors that affect training attendance is needed. There may be a role for computerised training programmes (e.g. BMJ Learning), with the integration of a scored online examination.

The training discussed in this chapter was carried out in all of the practices randomised to primary care parallel and primary care sequential prior to the trial.

# Chapter 4

# Delivering earlier antenatal screening for SCT in primary care: a cluster randomised controlled trial

This chapter is divided into five sections:

- section I – trial methods
- section II – primary outcome analysis
- section III – secondary outcomes analysis
- section IV – further analyses
- section V – discussion.

## Section I: trial methods

An abstract of the protocol for the trial is published on the Lancet website.[37] This, together with a copy of the full trial protocol, is included in Appendix 2.

### Design

A three-group randomised controlled trial was used, with general practices as the units of allocation. The trial evaluated (1) offering screening in primary care when women first report their pregnancies, with the aim of increasing the proportion of mothers tested in early pregnancy, and (2) offering parallel father testing with the aim of increasing the early detection of pregnancies requiring further investigation. Parallel father testing was explored as a potential addition to offering women SCT screening when they first report their pregnancies in primary care, with the aim of achieving the earliest possible gestational age at which couples know their carrier status.

### Setting

This is described in Chapter 2.

### Eligibility

- *Practices* were eligible for the trial if (1) they agreed to be randomised and (2) were able to provide anonymised data on all eligible pregnant women.
- *Pregnant women* were eligible for the trial if (1) they attended participating practices; (2) they wanted to continue their pregnancies; (3) their pregnancies were less than 19 weeks 6 days' gestation at their first visit to primary care; (4) their GP had no written record of SCT carrier status; and (5) there was a reliable estimate of gestational age based on LMP estimates of gestational age.
- *Fathers of babies* of eligible women in practices allocated to Group 1 (primary care, parallel testing) were eligible to be offered the test and to take part in the trial evaluation.
- *Participants* were eligible for the questionnaire or interview studies if they were at least 18 years old and consented to take part in the evaluation.

#### *Randomisation*

Study practices were allocated to intervention groups after they had agreed to participate and entered the run-in data collection period. The allocations for 27 practices were determined independently by Martin Gulliford, using minimisation. The MINIM programme was used.[38] The variables used for minimisation were PCT and number of partners at the practice (one or two, three or more).

### Intervention

Practices were allocated to one of three groups, differing in the ways in which testing was offered.

#### *Group 1: primary care with parallel father testing*

General practitioners, practice nurses and nurse practitioners offered the test to eligible pregnant women at their first visit in primary care to confirm the pregnancy. A verbal explanation was supplemented by written information produced by the NHS SC&T Screening Programme. Women wishing to be tested had a blood sample taken according to usual procedure in the practice. Women wanting more time for decision-making were invited to return within 1 week.

If the father was present, the test was offered at this time. If the father did not attend or was not

registered at the practice, women were invited to offer testing to the baby's father using a take-home pack. The pack contained information about the test, details of several local test centres (primary care, local hospital, SCT centre), and a request form. The fathers' samples were analysed as soon as they were received in the laboratory.

#### *Group 2: primary care, sequential testing*

Women were offered antenatal SCT screening when they first reported their pregnancies in primary care, as in Group 1. Fathers of babies of women in this study group were offered sequential testing, i.e. offered a test only if the mother of the baby was found to be a SCT carrier. The offer of testing to fathers was made by local sickle cell counsellors, in line with the NHS SC&T Screening Programme.

#### *Group 3: secondary care, sequential testing*

Women were offered antenatal SCT screening at the booking appointment. The booking appointment is the first antenatal check and is usually conducted by a community midwife. In the trial, this was conducted at the woman's home, in a community-based clinic or at a hospital. The fathers of the babies of the women in this study group were offered sequential testing, as described above. This was current standard care in Lambeth and Newham PCTs at the time of the trial.

## Outcome measures

Definitions for these measures and sources of data are outlined in *Table 3*.

#### *Primary outcome measure*

The primary outcome measure was the proportion of women screened before 70 days' gestation and this was available anonymously on *all* women who reported their pregnancies in trial practices during the study period. The timing of SCT screening was assessed by using the gestational age at test uptake. This was calculated from LMP to date of venesection for antenatal SCT screening. Anonymised data were collected from practices and were available for all eligible pregnancies.

Ultrasound scan (USS) estimates of gestational age provide more accurate measures of estimated date of delivery (EDD) than LMP estimates.[39,40] LMP estimates are limited by variability in cycle length and inaccuracies in estimations of LMP. Such variability is greatest for women under 25 and over 39 years of age.[39] In primary care the only estimates of gestational age available are based on LMP. In the SHIFT Trial we therefore opted to use LMP rather than USS to estimate gestational age at first visit and time of screening. Women with uncertain LMP dates were excluded from the analysis. There was no evidence to suggest that LMP would differ in accuracy across the three

***TABLE 3*** *Outcome measures for the SHIFT Trial*

| Outcome | Data from | Data available | Operationalisation |
|---|---|---|---|
| ***Primary*** | | | |
| Uptake of screening by mother < 70 days' gestation | Practice | Run-in and intervention | Date of blood sampling |
| ***Secondary*** | | | |
| Offer of screening to mother < 70 days' gestation | GP/woman | Intervention only | Date of GP or midwife offer |
| Time between pregnancy confirmation visit and screening (note: this is derived from other measures) | Practice | Run-in and intervention | Date of first visit and date of blood sampling |
| Mean gestational age at screening | Practice | Run-in and intervention | Date of blood sampling |
| Proportion of women tested who know father's carrier status by 77 days | Practice | Intervention only | Date by which tested women know the father's test result |
| Mother making an informed choice to have test (see Chapter 6) | Questionnaire | Intervention only | From questionnaire measure |

randomisation groups. Age difference (in age groups associated with variable cycle lengths) will be checked across randomisation groups.

#### *Secondary outcome measures*

- *Offer of screening to mother < 70 days* This was recorded in primary care records for intervention arms. For women in the standard care group these data were available only from women who completed a questionnaire ($n = 90$).
- *Time between pregnancy confirmation visit and screening.*
- *Mean gestational age at screening* Measured as time from LMP date to screening date.
- *Proportion of women who know the carrier status of the baby's father by 77 days (11 weeks)* This was assessed using the proportion of all women, regardless of carrier status, who know the carrier status of their baby's father by 77 days (11 weeks).

## Other measures

#### *Ethnicity*

Practices provided anonymous data on patient ethnicity, based generally on the 2001 Census categories. With consent, this was supplemented by self-reported data and data from maternity units and laboratories. The resulting ethnicity categories were grouped into the following categories: North European, South and South East Asian, African and African Caribbean, South European and Other European, Other ethnicity, Mixed ethnicity and Not known. These are consistent with the 'family origin questionnaire' used by the SCT Screening Programme. For trial analyses, ethnic origin was reduced to the categories of Northern European 'high-risk ethnic groups', including all other categories and 'not known'.

#### *Parity*

Practices provided anonymous data on parity.

#### *Socioeconomic status*

Data on neighbourhood levels of deprivation were obtained through participants' postcodes.

#### *Sample size calculation*

We estimated that we required data for 264 women attending eight general practices (33 women per practice) in each trial group to give sufficient power to detect a difference of between 30% and 50% in the proportion of women undergoing screening by 70 days' gestation in different trial arms, assuming 90% power and 5% significance. This assumed an intraclass correlation coefficient (ICC) of 0.03 based on a review of 31 studies in primary care, in which 75% of ICCs were less than 0.032 (11). Analysis of data from the run in data collection phase of the SHIFT Trial revealed an ICC of 0.036 for all women and 0.068 for eligible women. Repeating the initial sample size calculations using an ICC of 0.07 indicated data would be required from 1173 eligible women. Consequently, the data collection period was extended to 7 months at each practice.

## Analysis plan

An analysis plan was drawn up before the intervention phase data were available for analysis. The plan was discussed and agreed by the Data Monitoring and Ethics Committee [membership: Professor Max Parmar (Chair), Dr Simon Griffin, Dr Lyn Chitty].

#### *Analytic approach for effectiveness (Chapter 4) and cost-effectiveness data (Chapter 5)*

Analyses of the primary outcome were implemented using the method of generalised estimating equations (GEEs) because this facilitated adjustment for individual level characteristics and because the method, with appropriate modification, has been shown to offer accurate estimation and satisfactory confidence interval coverage even when there are small numbers of clusters.[41] A cluster level analysis of the practice-specific proportions was also implemented to facilitate estimation on a scale of differences in proportions.

#### *Eligibility for analysis*

According to the protocol, women were eligible for analysis if they presented for antenatal care in the study settings, wanted to proceed with the pregnancy, had a certain LMP date and if their carrier status was not documented in primary care records. Women aged under 18 were eligible to be offered the test according to the randomisation group but were ineligible to take part in the questionnaire study. They were included in the main analyses, but not included in the informed choice analyses. It was also decided to exclude women whose booking visit was equal to or more than 140 days (20 weeks) after the LMP date.

Women were therefore excluded from analyses if they were aged less than 18 years (informed choice analyses only); if the pregnancy confirmation visit was ≥ 140 days after the LMP date; if their

pregnancies miscarried before the mother was tested (once a date of testing was obtained no further data were collected on miscarriage or termination); if they had a termination of pregnancy before the mother was tested, unless the termination was for a fetal abnormality; or if the woman's carrier status was already known in primary care.

#### *Data for individual and practice characteristics*

Individual level data available for analysis included intervention phase data for women's age, parity and ethnicity. The same data were collected in the run-in phase, but ethnicity data were only available for about half of women, and data from the run-in phase were aggregated to practice level to summarise baseline screening performance, for example practice-specific proportion screened before 70 days' gestation in run-in phase. Data were also available for the number of GPs at the practice and PCT, which were used as stratifiers in the allocation.

#### *Analysis*

The primary outcome was whether each eligible woman had an SCT test performed before 70 days' gestation in intervention phase. Explanatory variables included trial group, age group, parity using the categories primiparous or multiparous, ethnic group using the categories of northern European, high-risk and not known, practice-specific proportion screened before 70 days in run-in phase, PCT, partnership size (1–2 or 3+). As the association of age with outcomes was not linear, age was grouped into the categories ≤ 24, > 24 to ≤ 28, > 28 to ≤ 32 and > 32 years.

The individual level analysis by logistic regression using the method of GEEs was regarded as the primary analysis. However, as the cluster level analysis led to estimation of the difference in proportion screened, the results from these analyses are also presented. Initially, we implemented a cluster level analysis, using linear regression of the practice-specific proportions on trial arm. The method of minimum variance weights was used to allow for varying number of eligible women between practices.[42] This led to estimation of the adjusted mean difference in screening uptake for each of the two primary-care-led screening groups in comparison with standard care. Then an individual level analysis was implemented in order to estimate the relative odds of screening uptake before 10 weeks for each of the two primary-care-led screening groups in comparison with standard care. Analyses were implemented using the 'xtgee' command in STATA version 9, specifying an exchangeable correlation matrix and the robust estimator of variance. In view of the modest number of practices included in the study, the standard error of the log odds was corrected for bias and a 'degrees-of-freedom correction' was applied in estimating *p*-values and confidence intervals. The 'bias correction' was implemented by inflating the standard error of the log odds by square root of m/(m–1), where 'm' is the number of clusters per group.[43] A 'degrees-of-freedom correction' was implemented by basing Wald tests and confidence intervals on quantiles of the *t* distribution rather than the normal distribution.[43] A simulation study has shown that these modifications give close to nominal confidence interval coverage, at least when small numbers of equal sized clusters are analysed.[41] Comparison of the adjusted individual level and cluster level analyses showed that these gave consistent results.

The same analytical framework was used for the other trial outcomes, including offer of screening to mother at < 70 days' gestation and time between pregnancy confirmation visit and screening. Methods were adapted for continuous outcomes as required.

## Procedure

#### *Inviting practices to participate in the trial*

All practices from two PCTs were invited to take part in the trial, using a research information sheet for practices (RISP). Invitations were sent to 123 practice managers, 450 GPs, 150 practice nurses and nurse practitioners. Expenses of approximately £3000 were available for participating practices. Participating practices and the research group signed research activity agreements (RAAs), detailing a payment schedule based on deliverables. The procedure is described in more detail in a published paper (Dormandy *et al.*, 2008 – see Appendix 1).[44]

#### *Testing in primary care*

Of the 25 practices completing the trial, nine offered blood testing in-house and 16 at off-site phlebotomy centres.

#### *Clinical follow-up of carriers*

Clinical follow-up of individuals found to be carriers was led by local SCT counsellors in line

with the NHS SC&T Screening Programme protocol.

#### *Consent to participate in the trial evaluation*

General practitioners asked all eligible women if their contact details could be made available to the research team. The research team contacted consenting women by telephone to explain the study and seek consent for participation in the evaluation. The procedure for seeking consent and ensuring a good response rate is described in Appendix 3 (Towards socially inclusive research: an evaluation of telephone questionnaire administration in a multilingual population).[45]

## Quality assurance

Fidelity to the research protocol was assessed by comparing maternity referrals with records of pregnancies sent to the research team. Fidelity to the clinical protocol in the intervention groups was assessed by comparing records of pregnancies sent to the research team with records of women offered testing in primary care. Discrepancies were discussed and resolved with participating practices.

## Ethical issues

Ethical approval was granted for the trial (05/Q0501/36). The trial interventions were at the cluster (practice) level through a modification to the practice system for antenatal care. As in most trials of cluster-level interventions, consent was obtained from the guardian of the cluster (PCT) on behalf of the cluster members (registered patients). The guardian's consent was considered ethically justified as the expected utility associated with the trial intervention was greater than the alternative.[46] As the data for the primary outcome (date of testing) were anonymised, there was no need for individual patient consent or for exemption under Section 60 of the Health and Social Care Act (2000).[47] Consent was sought for participation in the evaluation. In keeping with Medical Research Council (MRC) guidelines, women aged under 18 years were not invited to participate in the evaluation of the trial but were included in the primary outcome.

## Protocol changes

- *The main outcome data were collected for 7 months minimum, rather than 6 months* This was because the ICC of eligible women was observed to be 0.068, in contrast with the initial estimate of 0.03 (Progress Report 5).
- *Pilot studies* These were run in two practices in Lambeth and in Newham, rather than in one practice in Manchester.
- *Sample size for Time One questionnaires* The original protocol stated that we would collect questionnaire data on 100 women per group. This did not include an estimate for the effect of clustering, which indicated that we would require 29 completed questionnaires per cluster.
- *Place of phlebotomy in practices randomised to Groups 1 or 2* As some practices were unable to offer on-site phlebotomy, the protocol was changed to state that blood would be taken using usual phlebotomy procedure in the practice, rather than being taken by the GP or practice nurse.
- *Sample size for women's interviews* The submitted proposal erroneously stated that 120 women would complete Time Two questionnaires, and would be interviewed. We meant to say 120 women would complete Time Two questionnaires, and we would interview 20 women.
- *Clarification of eligibility criteria for practices* Eligible practices had to agree to be randomised to any one of the three groups.
- *Eligibility of women* The definition of the eligibility of women was changed to specify the gestational age at the first visit to the GP.

## Participants

*Figure 3* shows a CONSORT flow diagram, illustrating the flow of participants through the SHIFT Trial.

#### *Practices*

There were 123 practices in the two PCTs, and four did not agree to randomisation. This resulted in 119 eligible practices being invited to participate in the trial. There were 29 practices that participated in the trial, with two serving as pilot sites. Of the 27 practices that were randomised, two withdrew, and 25 completed the trial (*Figure 3*). It was not possible to obtain data from the practices that withdrew from the study, so an intention-to-treat analysis was not feasible. Data from the run-in phase are described in Chapter 2. In analyses for Chapter 4, we additionally excluded women who confirmed their pregnancies after 20 weeks' gestation, giving 1390 women from the run-in phase as eligible to contribute to trial analyses.

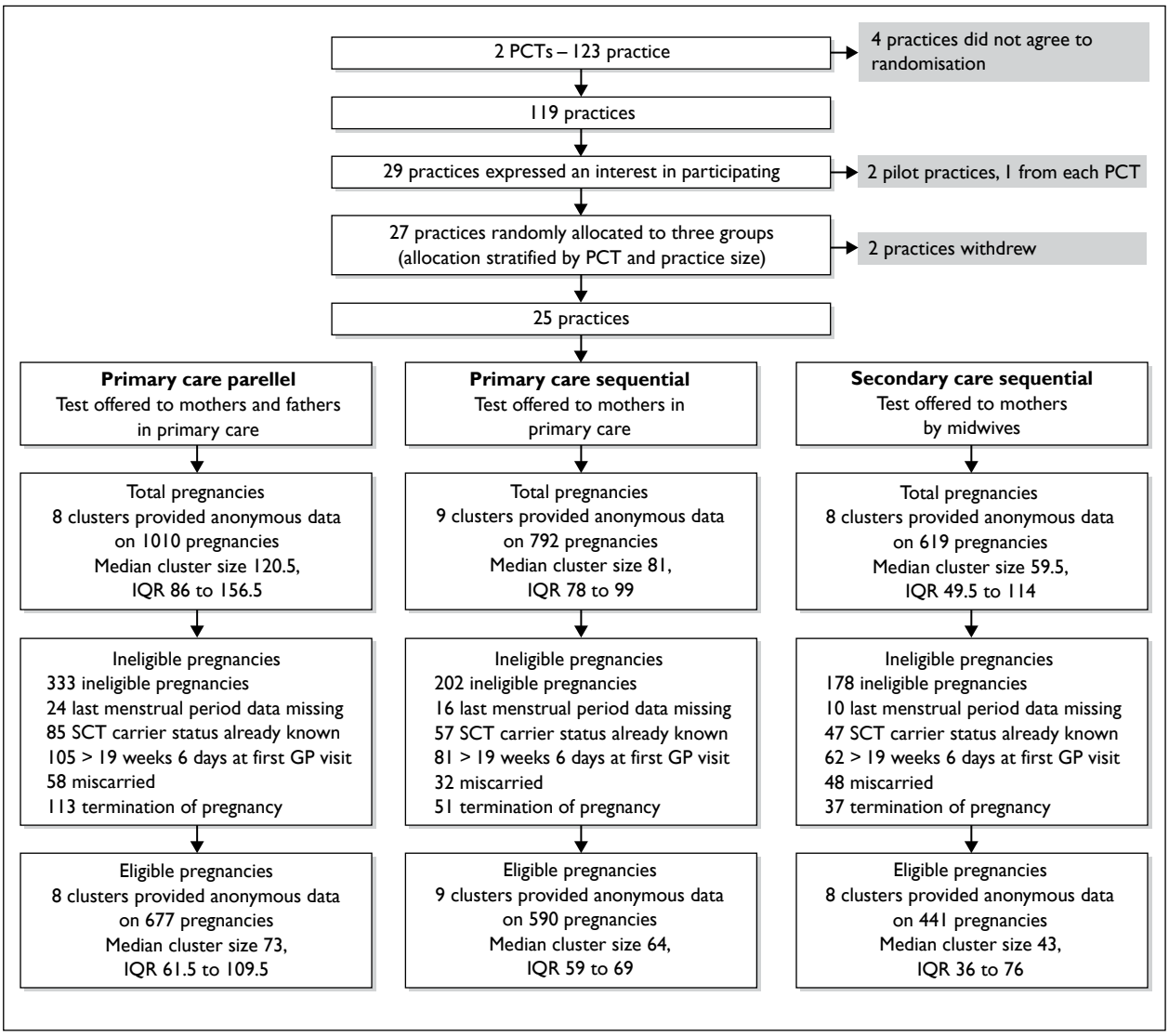


***FIGURE 3*** *CONSORT diagram of flow of participants through SHIFT.*

### *Pregnant women*

In the intervention phase, there were 2421 pregnancies identified in the 25 practices. Of these, 1708 pregnancies were eligible to be assessed for the primary outcome measure (*Figure 3*). There were 17 women with more than one pregnancy but only one woman was eligible for analysis in both pregnancies.

Cases excluded from the analysis:

- LMP was not known ($n = 50$).
- Carrier status was already known, i.e. recorded patient's notes in primary care ($n = 189$).
- Termination of pregnancy for reasons other than fetal abnormality ($n = 201$).
- Miscarriage ($n = 138$).
- Pregnancy confirmation visit was after 20 weeks' gestation ($n = 248$).

There were 87 women who were excluded on two or more criteria. There were 41 women who had a miscarriage after SCT testing and 28 women who had a termination of pregnancy after SCT testing and these were included.

## Characteristics

The characteristics of trial practices and participants recruited in the run-in and intervention phases of the trial are shown in *Table 4*. There were no differences between the trial groups in age, parity or proportion confirming pregnancy before 70 days. There were differences

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***TABLE 4*** *Characteristics of participants*

| Setting | Secondary care sequential | Primary care | | *p*-value[a] |
|---|---|---|---|---|
| | | Parallel | Sequential | |
| ***General practices*** | ***8*** | ***8*** | ***9*** | |
| PCT A : PCT B | 4:4 | 4:4 | 5:4 | Stratifier |
| GPs at practice 1–2:≥3 | 3:5 | 3:5 | 3:6 | Stratifier |
| ***Run-in phase*** | | | | |
| Eligible participants | 336 | 594 | 460 | |
| Pregnancy confirmation visit <70 days' gestation (*n*, %) | 255 (76) | 458 (77) | 347 (75) | 0.941 |
| Screening test performed <70 days' gestation (*n*, %) | 12 (4) | 39 (7) | 12 (3) | 0.275 |
| Gestational age at screening (days, mean IQR)[b] | 111 (91 to 130) | 104 (87 to 120) | 110 (88 to 129) | 0.318 |
| Pregnancy confirmation to screening (days, mean IQR)[b] | 53 (34 to 72) | 48 (32 to 63) | 49 (36 to 65) | 0.460 |
| ***Intervention phase*** | | | | |
| All participants[c] | 619 | 1010 | 792 | |
| Eligible participants[c,d] (*n*, %) | 441 (71) | 677 (67) | 590 (74) | |
| Age (years, median, IQR) | 28.0 (23.6 to 32.8) | 28.0 (23.9 to 32.2) | 29.1 (25.2 to 33.8) | 0.250 |
| Primiparous (*n*, %) | 241 (55) | 392 (58) | 307 (52) | 0.650 |
| Pregnancy confirmation visit <70 days' gestation (*n*, %) | 323 (73) | 505 (75) | 464 (79) | 0.386 |
| Ineligible participants[c] | | | | |
| LMP date missing | 10 | 24 | 16 | |
| Termination of pregnancy | 37 | 113 | 51 | |
| Miscarriage | 48 | 58 | 32 | |
| Carrier status known | 47 | 85 | 57 | |
| First visit ≥ 140 days' gestation | 62 | 105 | 81 | |

a Test for difference between groups.
b Based on 956 women who were screened before 182 days gestation.
c Eighty-seven subjects had two or more exclusion criteria.
d Figures are frequencies (per cent of all subjects).
Figures are frequencies (per cent of eligible participants in group), except where indicated.

***TABLE 5*** *Ethnicity of participants*

| Ethnicity category | Secondary care sequential | Primary care | |
|---|---|---|---|
| | | Parallel | Sequential |
| North European | 76 (17) | 101 (15) | 121 (21) |
| South and South East Asian | 93 (21) | 103 (15) | 224 (38) |
| African and African Caribbean | 84 (19) | 180 (27) | 93 (16) |
| South European and Other European | 70 (16) | 138 (20) | 72 (12) |
| Other ethnicity | 14 (3) | 25 (4) | 22 (4) |
| Mixed ethnicity | 12 (3) | 13 (2) | 13 (2) |
| Not known | 92 (21) | 117 (17) | 45 (8) |

Figures are frequencies (per cent of eligible participants).

by ethnicity ($p = 0.001$) with a higher proportion of South and South East Asian women in primary care sequential than the other trial groups, and more African and African Caribbean women in primary care parallel than the other trial groups (*Table 5*). In the run-in phase, screening uptake before 70 days was 7% in the practices assigned to primary care parallel testing compared with 4% for standard care and 3% for primary care sequential. Even though the differences in baseline screening uptake were not statistically significant, they assume importance in the estimation of adjusted effect measures.

# Section II: primary outcome

## Primary outcome measure: time of uptake and proportion screened

In both intervention groups, more women were screened before 70 days' gestation than in the standard care group (*Table 6*, and *Figures 4* and *5*). *Table 6a* gives the primary outcome by family practice and group. *Table 7* shows the cumulative proportion of women screened by gestational age and trial arm.

After adjusting for age group, parity, family origin risk status, screening uptake in the run-in phase, partnership size and PCT, the increase in screening uptake was 16.5% (95% CI 7.1 to 25.8, $p = 0.002$) for primary care parallel, and 27.8% (95% CI 14.8 to 40.7, $p < 0.001$) for primary care sequential (*Table 8*). Adjustment for baseline screening performance had a larger impact on the estimates for the parallel testing group because screening uptake in the run-in phase was highest in this group. There was no difference in the proportion of women screened before 70 days' gestation between the two primary care groups: offering parallel father testing neither facilitated nor impeded maternal SCT testing uptake (*Table 8a*).

# Section III: secondary outcomes

## Offer of screening

In both trial arms, more women were offered screened before 70 days' gestation than in the standard care group (*Table 6*). Date on offer for the standard care group was available for only 90 women.

After adjusting for maternal age group, parity, 'higher-risk' family origin, partnership size, PCT and clustering by practice, the increase in the proportion offered the test before 70 days were 39.2% (95% CI 26.0 to 52.4, $p < 0.001$) for primary care parallel and 44.2% (95% CI 26.6 to 61.9, $p = -0.001$) for primary care sequential (*Table 8*).

### *Time between pregnancy confirmation visit and screening*

The mean delay between the pregnancy confirmation visit and screening was 60 days in standard care, 35 days in primary care parallel and 31 days in primary care sequential trial arms. Offering screening in primary care reduced the average delay between GP visit and screening uptake by nearly 3 weeks (*Tables 8* and *9*). *Figure 5* shows uptake of screening tests by time since pregnancy-confirmation consultation in primary care; 31% of women in the PC-parallel group, and 35% in PC-sequential group, were tested within 2 weeks of pregnancy confirmation visit compared with 4% in standard care.

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***TABLE 6a*** *Screening outcomes by intervention group*

| | Frequency (%) | | |
|---|---|---|---|
| | **Standard care (441)** | **Primary care parallel (677)** | **Primary care sequential (590)** |
| Women's uptake of screening test <70 days' gestation | 9 (2) | 161 (24) | 167 (28) |
| Women's uptake of screening before 182 days' gestation | 324 (73) | 571 (84) | 481 (82) |
| Offer of screening test before 70 days' gestation | 3/90[a](3) | 321 (47) | 281 (48) |
| Delay from pregnancy confirmation visit to screening uptake [days, mean (IQR)][b] | 60 (42 to 79) | 35 (7 to 59) | 31 (5 to 54) |
| Gestational age at screening uptake[b] [days, mean (IQR)] | 118 (101 to 134) | 94 (66 to 118) | 90 (61 to 113) |

a In the standard care group, offer of test was ascertained for questionnaire respondents only.
b In women who were screened before 182 days (26 weeks' gestation).
Figures are frequencies (column per cent), except where indicated.

***TABLE 6b*** *Primary outcome by family practice and group*

| **Secondary care** | | | **Family practice parallel partner** | | | **Family practice sequential partner** | | |
|---|---|---|---|---|---|---|---|---|
| **Practice ID** | **Screened run-in (%)** | **Screened intervention (%)** | **Practice ID** | **Screened run-in (%)** | **Screened intervention (%)** | **Practice ID** | **Screened run-in (%)** | **Screened intervention (%)** |
| A | 2/37 (5) | 1/33 (3) | I | 2/33 (6) | 7/33 (21) | Q | 3/49 (6) | 9/59 (15) |
| B | 4/33 (12) | 4/36 (11) | J | 4/73 (5) | 5/62 (8) | R | 1/52 (2) | 7/56 (13) |
| C | 4/70 (6) | 3/85 (4) | K | 20/90 (22) | 35/84 (42) | S | 0/30 (0) | 21/62 (34) |
| D | 1/35 (3) | 0/44 (0) | L | 1/32 (3) | 2/61 (3) | T | 0/61 (0) | 23/64 (36) |
| E | 0/32 (0) | 0/98 (0) | M | 4/146 (3) | 39/156 (25) | U | 7/55 (13) | 10/54 (19) |
| F | 0/32 (0) | 1/36 (3) | N | 4/41 (10) | 22/62 (35) | V | 0/45 (0) | 47/75 (63) |
| G | 0/35 (0) | 0/42(0) | O | 0/57 (0) | 25/108 (23) | W | 0/37 (0) | 29/69 (42) |
| H | 1/62 (2) | 0/67 (0) | P | 4/122 (3) | 26/111 (23) | X | 0/64 (0) | 13/87 (15) |
| | | | | | | Y | 1/67 (1) | 8/64 (13) |
| | 12/336 (4) | 9/441 (2) | | 39/594 (7) | 161/677 (24) | | 12/460 (3) | 167/590 (28) |

Figures are number of subjects screened <70 days' gestation/number of eligible subjects at practice (row per cent).

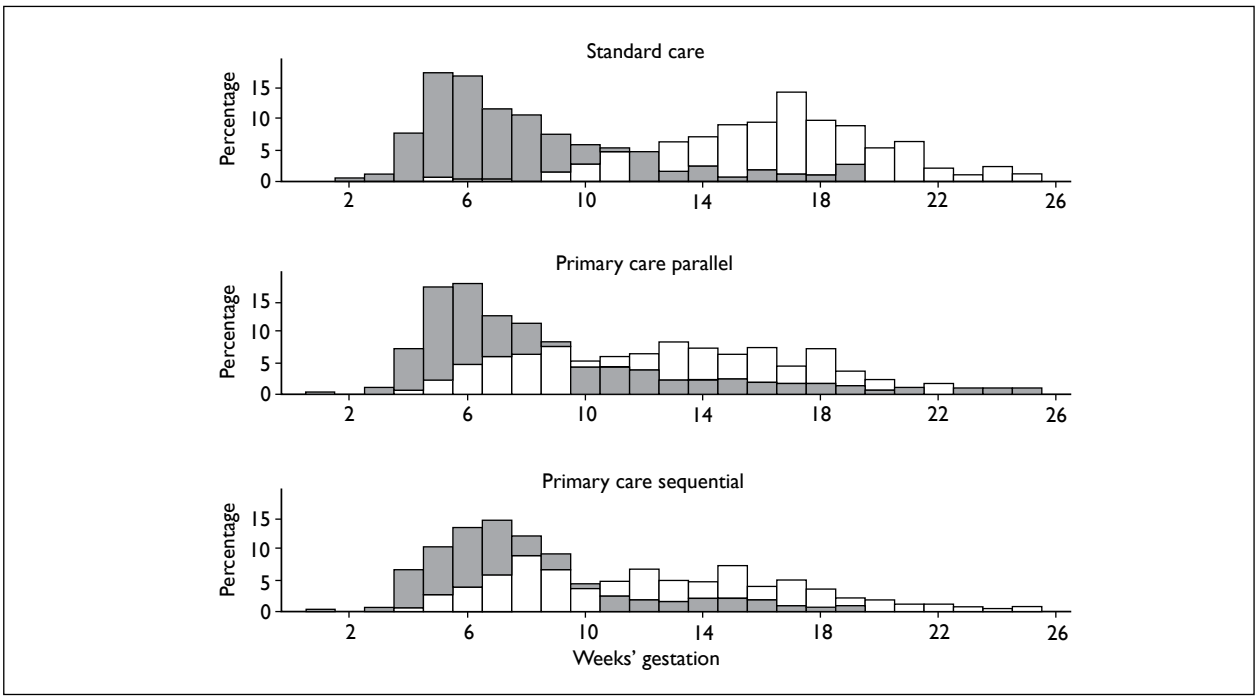


***FIGURE 4*** *Distributions for gestational age at first pregnancy-confirmation consultation (black bars) and at sickle cell and thalassaemia screening (white bars) by randomisation group. The proportions not screened by 26 weeks' gestation were: standard care, 27%; primary care parallel, 16%; and primary care sequential 18%.*

#### *Mean gestational age at screening (measured as time from LMP date to screening date)*

The mean gestational age at screening was 118 days (16 weeks and 6 days) in standard care, 94 days (13 weeks and 3 days) in primary care parallel and 90 days (12 weeks and 6 days) in for primary care sequential trial arms. After adjusting for the variables listed above and mean gestational age at screening in the run-in phase, the differences from standard care were between 2 weeks for primary care parallel ($p = 0.008$), and three weeks ($p = 0.003$) for for primary care sequential (*Tables 8* and *9*).

## Proportion of women tested who knew father's carrier status by 77 days

The screening uptake of fathers was 51/677 (8%) in primary care with parallel testing, and 16/590 (3%) in primary care with sequential testing and 13/441 (3%) in standard care. The proportion (%, *p*-value) of women who knew the carrier status of the baby's father by 77 days (11 weeks) was: 0/441 (0%) in standard care, 13/677 (2%, 0.003) in primary care with parallel testing and 3/590 (1%, 0.374) in primary care with sequential testing.

## Pattern of screening uptake

By 26 weeks' gestation, the proportions of women screened in all three groups were similar (*Tables 7–9*).

There were no differences in secondary outcomes between the intervention trial arms (*Table 8a*).

## Testing of maternal carriers and fathers

#### *Testing of SCT carrier mothers*

Among 2421 pregnancies, there were 160 women identified as SCT carriers. After excluding 17 women who met other criteria for ineligibility, there were 50 women whose carrier status was already known and 93 women who were newly identified as carriers in this trial (*Figure 6*). One woman, whose screening test was at 183 days' gestation, and another woman, whose test did not originate in primary care, were included as newly identified carriers.

The characteristics of carrier women are shown in *Table 10*. There were five women whose ethnicity was given as 'British', who were coded as 'Northern European'. Women of African or Caribbean ethnicity accounted for more than half of carriers. Women of South and South East Asian ethnicity

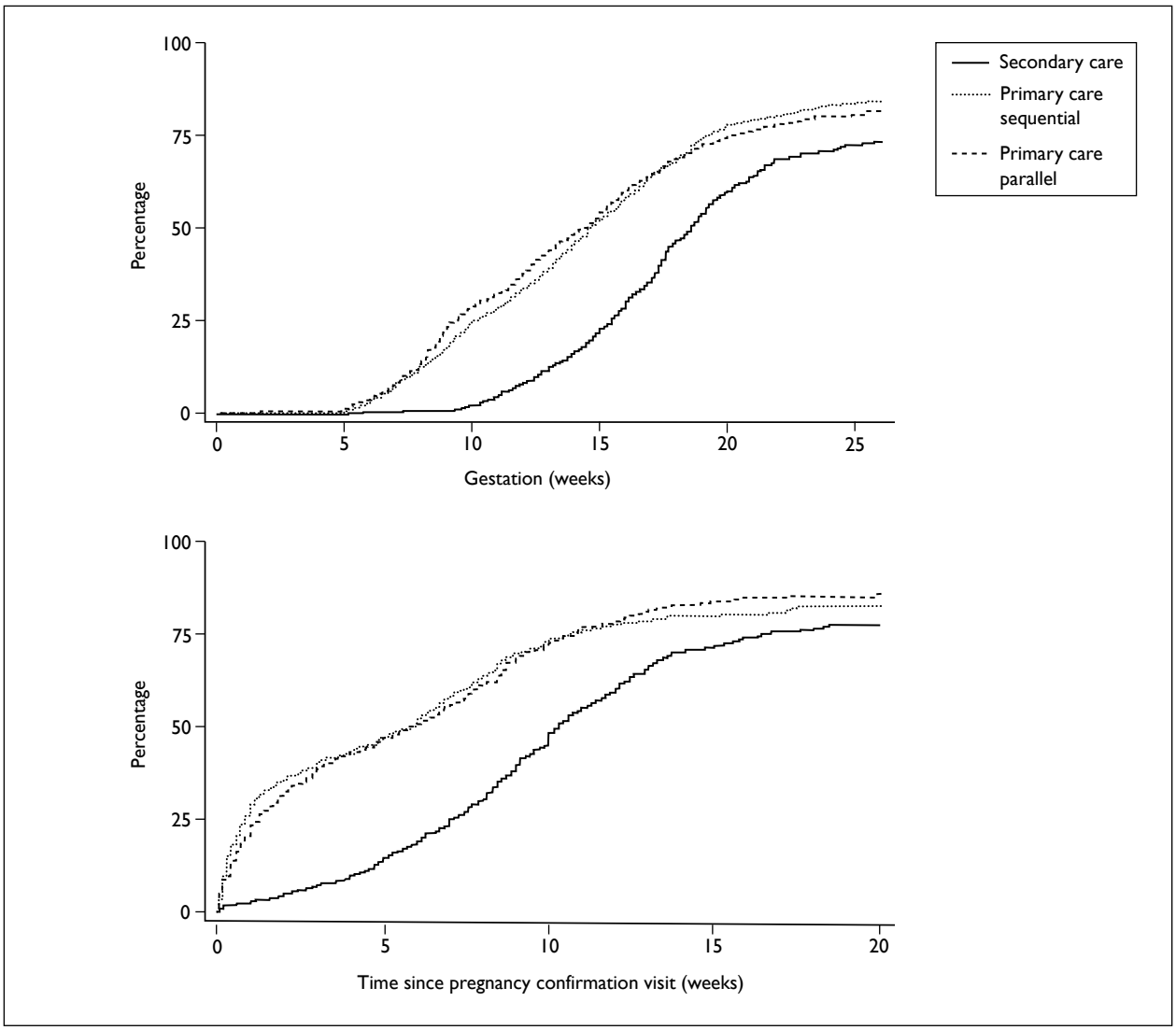


***FIGURE 5*** *Uptake of screening by gestational age (a) and by time since pregnancy-confirmation consultation in primary care (b).*

accounted for the next largest group, with 10 'Bangladeshi, five 'Indian' and five 'Pakistani' carriers. The distribution of carrier women by age and parity was generally similar to the overall sample.

*Table 11* shows the distribution of carrier mothers by intervention group. As the numbers of observations were small, *p*-values were estimated using exact logistic regression in STATA version 10, assuming clustering by practice to be negligible. Carrier mothers were more likely to be tested before 70 days' gestation when SCT testing was offered in primary care. In the primary care parallel group, 12/47 carriers (26%) were tested before 70 days' gestation ($p = 0.079$), with 11/25 (44%) in the primary care sequential group ($p = 0.005$), compared with 1/21 (5%) in the standard care group. Combining the two primary care groups together, the relative odds of a maternal carrier being tested before 70 days' gestation were 9.24 (1.31 to 405.7) $p = 0.017$.

These analyses were performed using exact logistic regression because some cell frequencies were small and logistic regression may give biased results under this condition. The ICC for screening uptake before 70 days among carrier mothers only, by analysis of variance, was 0.02. This suggests that clustering should not be ignored. However, when ordinary logistic regression with robust variance estimates was implemented, the estimated *p*-value for the difference in screening uptake before 70 days in primary care parallel group, compared with standard care, was $p = 0.044$ and for the primary care sequential group, $p = 0.003$. Therefore, under these conditions, exact logistic regression appears to offer more conservative estimates.

***TABLE 7*** *Cumulative uptake of screening tests by gestational age and intervention group*

| Gestational age (completed weeks) | Uptake percentage (frequency) | | |
|---|---|---|---|
| | Standard care (441) | Primary care parallel (677) | Primary care sequential (590) |
| 0–1 | 0 | 0.2 (1) | 0 |
| 2–3 | 0 | 0 | 0.3 (2) |
| 4–5 | 0.5 (2) | 2.7 (18) | 3.7 (22) |
| 6–7 | 1.0 (4) | 12.0 (81) | 13.2 (78) |
| 8–9 | 2.0 (9) | 23.8 (161) | 28.3 (167) |
| 10–11 | 7.9 (35) | 33.4 (226) | 36.8 (217) |
| 12–13 | 16.3 (72) | 45.6 (309) | 48.1 (284) |
| 14–15 | 28.3 (125) | 57.6 (390) | 59.8 (353) |
| 16–17 | 45.8 (202) | 67.8 (459) | 68.6 (405) |
| 18–19 | 59.6 (263) | 77.3 (523) | 74.4 (439) |
| 20–21 | 68.5 (302) | 80.4 (544) | 77.8 (459) |
| 22–23 | 70.7 (312) | 82.9 (561) | 80.2 (473) |
| 24–25 | 73.5 (324) | 84.3 (571) | 81.5 (481) |
| Not screened | 117 | 106 | 109 |

#### *Uptake of SCT screening tests by fathers*

There were 84 cases with father testing results available, 74 of these also had data for date of testing; the test date was before the LMP in four cases which were excluded from analysis, leaving 80 father tests for analysis with 70 cases in which date of father testing known. The striking feature of the results, therefore, was the low uptake of father screening with 8% fathers tested in the primary care parallel testing group and 3% in both of the sequential testing groups. Based on these small numbers, fathers were more likely to be tested before 77 days' gestation in the primary care parallel testing group as required by the protocol (*Table 11*).

Among fathers whose partners were carrier mothers, the uptake of father screening was higher than among all fathers, being 9/21 (44%) in standard care, 19/47 (40%) in primary care parallel testing and 11/25 (44%) in primary care sequential testing, with no overall difference among groups. Father testing before 77 days' gestation, if the mother was a carrier, was performed for 0/21 (0%) in standard care, 3/47 (6%) in primary care parallel testing and 3/25 (12%) in primary care sequential (*Table 11*). If the mother was not a carrier then father testing was more frequent before 77 days' gestation in the primary care parallel testing group, as required by the protocol, but only 13 (2%) of such fathers in this group were tested before 77 days' gestation.

#### *Test results in carriers identified in the trial*

*Table 12* shows the results of SCT testing in carrier women.

## Section IV: further analyses

A number of additional analyses were implemented to evaluate intervention effects in subgroups of participants and to evaluate possible interactions. The results of these analyses were generally negative and it was not considered important to present all the analyses in detail. The main findings are summarised below. Further details are available from the authors of the report.

### Trial outcomes by ethnic group

The distribution of the sample by ethnic group is shown in *Table 5*. For further analysis, women were divided into three groups: (1) 'Northern European'; (2) 'High risk', including African and African Caribbean, South and South East Asian, South European and Other European, Other ethnicity and Mixed ethnicity; and (3) 'Not known'. In general, women of 'high-risk' ethnicity had slightly greater uptake of screening before 70 days' gestation. Overall uptake of screening before 182 days' gestation was similar in Northern Europeans and women of 'high-risk' ethnicity. After adjusting for age group, parity, partnership size, PCT,

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***TABLE 8a*** *Estimated effect of intervention on screening outcomes, cluster level analysis in primary care*

| | | Parallel (677) | | Sequential (590) | |
|---|---|---|---|---|---|
| **Setting** | | **Estimate (95% CI)** | ***p*-value** | **Estimate (95% CI)** | ***p*-value** |
| Uptake of screening test before 70 days' gestation | Adjusted per cent difference[a] | 16.5 (7.12 to 25.8) | 0.002 | 27.8 (14.8 to 40.7) | <0.001 |
| Uptake of screening before 182 days' gestation | Adjusted per cent difference[b] | 3.80 (–7.93 to 15.54) | 0.502 | 9.83 (–2.30 to 22.0) | 0.105 |
| Offer of screening test before 70 days' gestation | Adjusted per cent difference[c] | 39.2 (26.0 to 52.4) | <0.001 | 44.2 (26.6 to 61.9) | <0.001 |
| Time from pregnancy confirmation to screening | Adjusted mean difference (days)[d] | –18.0 (–26.3 to –9.7) | <0.001 | –21.5 (–32.5 to –10.4) | 0.001 |
| Gestational age at screening | Adjusted mean difference (days)[e] | –15.5 (–26.4 to –4.63) | 0.008 | –21.8 (–34.8 to –8.80) | 0.003 |

a Adjusted for Model 1 and proportion screened before 70 days' gestation in run-in period.
b Adjusted for Model 1 and uptake of screening before 182 days in the run-in period.
c Adjusted for Model 1: age group, parity, proportion of 'high-risk' ethnic groups, PCT and number of GP partners at practice.
d Adjusted for Model 1 and mean time interval from pregnancy confirmation to screening in the run-in period.
e Adjusted for Model 1 and mean gestational age at screening in the run-in period.

***TABLE 8b*** *Estimated difference between primary care parallel and primary care sequential trial arms, cluster level analysis*

| | | Difference between active intervention arms | |
|---|---|---|---|
| | | **Estimate (95% CI)** | ***p*-value** |
| Uptake of screening test before 70 days' gestation | Adjusted per cent difference[a] | 13.5 (–4.3 to 31.4) | 0.119 |
| Uptake of screening before 182 days' gestation | Adjusted per cent difference[b] | –6.08 (–21.6 to 9.48) | 0.399 |
| Offer of screening test before 70 days' gestation | Adjusted per cent difference[c] | 3.98 (–16.5 to 24.4) | 0.674 |
| Time from pregnancy confirmation to screening | Adjusted mean difference (days)[d] | –3.84 (–16.7 to 9.01) | 0.516 |
| Gestational age at screening | Adjusted mean difference (days)[e] | 6.05 (–4.88 to 16.9) | 0.242 |

a Adjusted for Model 1 and proportion screened before 70 days' gestation in run-in period.
b Adjusted for Model 1 and uptake of screening before 182 days in the run-in period.
c Adjusted for Model 1: age group, parity, proportion of 'high-risk' ethnic groups, PCT and number of GP partners at practice.
d Adjusted for Model 1 and mean time interval from pregnancy confirmation to screening in the run-in period.
e Adjusted for Model 1 and mean gestational age at screening in the run-in period.

***TABLE 9*** *Estimated effect of intervention on screening outcomes, individual level analysis using GEEs in primary care*

| | | Parallel | | Sequential | |
|---|---|---|---|---|---|
| **Setting** | | **Estimate (95% CI)** | ***p*-value** | **Estimate (95% CI)** | ***p*-value** |
| Uptake of screening test before 70 days' gestation | Adjusted odds ratio[a] | 10.1 (3.66 to 27.7) | <0.001 | 18.1 (6.66 to 49.0) | <0.001 |
| Uptake of screening before 182 days' gestation | Adjusted odds ratio[b] | 1.26 (0.70 to 2.26) | 0.410 | 1.30 (0.79 to 2.12) | 0.275 |
| Offer of screening test before 70 days' gestation | Adjusted odds ratio[c] | 28.0 (7.67 to 102.1) | <0.001 | 29.0 (7.45 to 113.2) | <0.001 |
| Time from pregnancy confirmation to screening | Adjusted mean difference (days)[d] | –19.4 (–26.6 to –12.2) | <0.001 | –24.6 (–31.8 to –17.3) | <0.001 |
| Gestational age at screening | Adjusted mean difference (days)[e] | –16.7 (–24.9 to –8.46) | <0.001 | –24.2 (–32.7 to –15.6) | <0.001 |

a Adjusted for Model 1 and proportion screened before 70 days' gestation in run-in period.
b Adjusted for Model 1 and uptake of screening before 182 days in the run-in period.
c Adjusted for Model 1: age group, parity, proportion of 'high-risk' ethnic groups, PCT and number of GP partners at practice.
d Adjusted for Model 1 and mean time interval from pregnancy confirmation to screening in the run-in period.
e Adjusted for Model 1 and mean gestational age at screening in the run-in period.

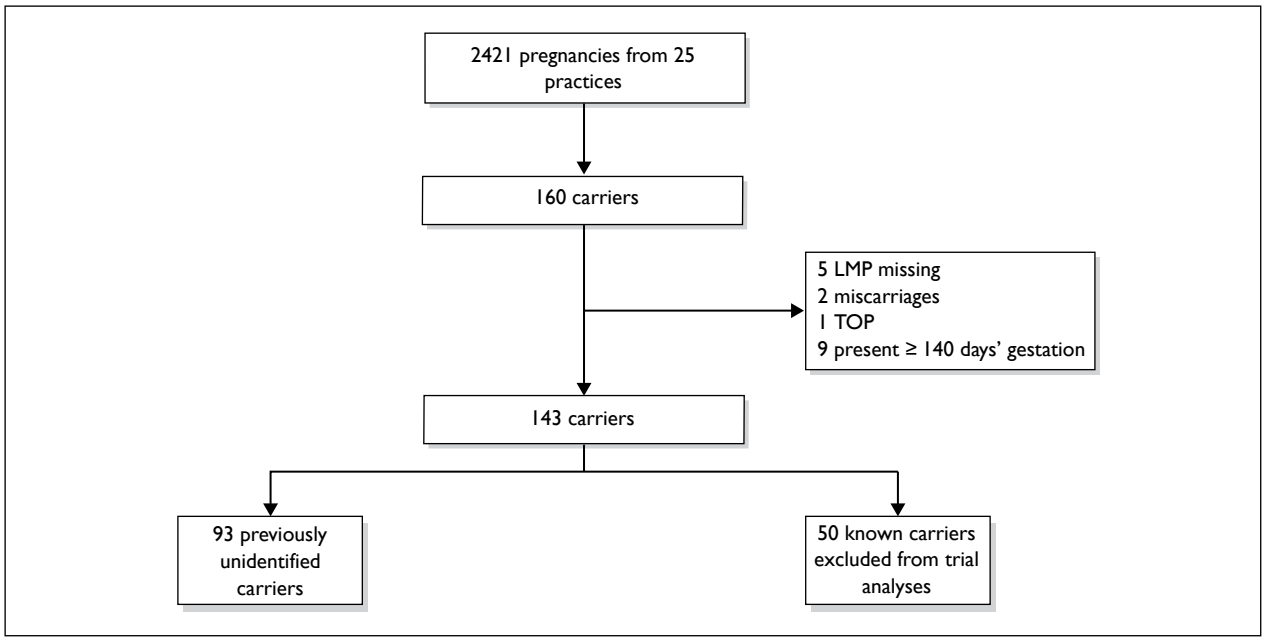



***FIGURE 6*** *Flow chart showing women identified as carriers.*

baseline screening performance and clustering by practice, ethnicity was not associated with uptake of screening before 70 days' gestation, uptake of screening before 182 days' gestation, and mean gestational age at screening uptake. However, in adjusted analyses, women of 'higher-risk' family origin had a shorter delay from pregnancy confirmation visit to testing – the mean difference from Northern Europeans was about 7 days.

## Trial outcomes by age group

In general, younger mothers aged 24 years and under showed about 6% lower uptake of screening before 70 days' gestation, and the mean gestational age at screening was later than for older mothers aged more than 32 years. This was associated with later pregnancy confirmation visits among the younger mothers who, on average, confirmed

***TABLE 10*** *Characteristics of women newly identified as carriers during the trial*

| | Frequency (%) |
|---|---|
| Ethnicity | |
| North European | 5 (4) |
| South and South East Asian | 20 (14) |
| African or Caribbean | 82 (57) |
| South European | 2 (1) |
| Other | 5 (4) |
| Mixed | 6 (4) |
| Not known | 23 (16) |
| Primiparous | 77 (54) |
| Age group (years) | |
| < 24 | 32 (22) |
| 24–28 | 34 (24) |
| 28–32 | 38 (27) |
| ≥ 32 | 39 (27) |

their pregnancies about 10 days later than older mothers.

## Trial outcomes by parity, partnership size and PCT

Screening outcomes were generally similar for primiparous and multiparous women. The uptake of SCT screening varied widely between practices in the intervention phase (*Table 6b*). Women attending practices with one or two partners generally had more favourable screening outcomes than women attending practices with three or more partners, but this pattern of results was not consistent across trial arms. Women attending PCT-B practices generally had slightly more favourable screening outcomes than women attending PCT-A practices.

## Interaction analyses

In general, there was no evidence that intervention effects varied between subgroups of the sample. There was evidence that the association of screening uptake before 70 days in the run-in phase with intervention effect varied in the different intervention groups. This may be explained by the observation that some practices with very low screening uptake in the run-in period showed very high uptake in the intervention phase. There was evidence that the association of screening uptake < 182 days' gestation with age group differed by trial arm. This was not considered to be a clinically significant finding. In the primary care sequential group, there was evidence that mothers with 'high-risk' ethnicity were screened earlier in pregnancy with shorter delays. Evaluation of data from individual practices suggested that this pattern of association may be accounted for by practices 32 and 36, which had very high proportions of ethnic minority women and unusually short time intervals to screening in the intervention phase.

## Intraclass correlation coefficients

Intraclass correlation coefficients (ICCs) for the main outcome measures were estimated by analysis of variance. The ICC for a binary variable is associated with prevalence. The effect of the intervention was therefore generally to increase the value of the ICC. ICCs were therefore estimated by trial arm, and estimates are imprecise as a result of the small number of practices included in each trial arm. The results are shown in *Table 14*. We caution that these results may have limited generalisability.

# Section V: discussion

## Summary of main conclusions drawn from these results

- Offering antenatal SCT screening at the pregnancy-confirmation consultation in primary care is associated with an increased proportion of women being screened before 10 weeks' gestation. In quantitative terms, the increase is from 2% to 27%. The reduction in delay between pregnancy being confirmed and screening test being performed is nearly 3 weeks.
- Offering antenatal SCT screening at the pregnancy-confirmation consultation in primary care does not have any impact on overall uptake of SCT screening over the first 26 weeks of pregnancy.
- The overall uptake of father SCT testing is less than 5%.
- Offering parallel testing to the baby's father at the pregnancy confirmation visit appears to facilitate earlier testing of fathers. However, in view of the overall low test uptake among fathers, parallel testing does not appear to be a useful strategy for SCT testing in this setting.
- Fewer than 5% of couples, in which the woman was a carrier, are made aware of their couple carrier status before 11 weeks' gestation across all trial arms.
- Uptake of SCT screening by pregnant women is equitable with respect to ethnic origins but

***TABLE 11*** *Identification of SCT carrier women and father testing by trial arm*

| | | Primary care parallel | | Primary care sequential | |
|---|---|---|---|---|---|
| | **Standard care** | **Frequency (%)** | ***p*-value[a]** | **Frequency (%)** | ***p*-value[a]** |
| ***Eligible women*** | ***441*** | ***677*** | | ***590*** | |
| Couple carrier status known if mother carrier | 8/21 (38) | 18/47 (38) | 1.000 | 12/25 (48) | 0.708 |
| Couple carrier status known <77 days' gestation if mother carrier | 0/21 (0) | 2/47 (4) | 0.949 | 2/25 (8) | 0.580 |
| Mother identified carrier | 21 (5) | 47 (7) | | 25 (4) | |
| Mother identified carrier, tested <70 days' gestation | 1/21 (5) | 12/47 (26) | 0.079 | 11/25 (44) | 0.005[b] |
| Fathers tested | 13 (3) | 51 (8) | | 16 (3) | – |
| Fathers tested <77 days' gestation | 0 (0) | 16 (2) | <0.001 | 4 (1) | 0.214[c,d] |
| Mother identified carrier: father tested | 9/21 (43) | 19/47 (40) | 1.000 | 11/25 (44) | 1.000 |
| Mother identified carrier: father tested <77 days' gestation | 0/21 (0) | 3/47 (6) | 0.647 | 3/25 (12) | 0.303[c,d] |
| Mother not carrier: father tested | 4/420 (1) | 32/630 (5) | – | 5/565 (1) | – |
| Mother not carrier: father tested <77 days' gestation | 0/420 (0) | 13/630 (2) | 0.003 | 1/565 (0) | 1.000[c,d] |
| Couple carrier status known, all women | 12 (3) | 50 (7) | <0.001 | 17 (3) | 1.000 |
| Couple carrier status known <77 days' gestation, all women | 0 | 13 (2) | 0.003 | 3 (1) | 0.374[d] |

a *p*-values were estimated by exact logistic regression because cell frequencies were small and were not adjusted for possible clustering.
b There were 93 carriers identified but one was tested at 183 days gestation and one was Newham SCT screen only.
c There were 84 fathers tested but only 74 of these had known dates of testing and four of these had dates of testing before LMP.
d Based on cases with known date of testing and testing not before LMP.
e There was one couple with status known date before LMP and this was omitted.
Figures are frequencies (per cent of column total except where shown).

***TABLE 12*** *Test results for women identified either as carriers or having abnormal haemoglobins*

| Condition | Carriers identified in trial | Carrier status known | Total |
|---|---|---|---|
| AS | 50 | 30 | 80 |
| AC | 15 | 7 | 22 |
| AD | 5 | – | 5 |
| AE | 4 | 2 | 6 |
| SS | 1 | – | 1 |
| SC | 1 | – | 1 |
| EE | 1 | – | 1 |
| Alpha thalassaemia carrier | 3 | 5 | 8 |
| Beta thalassaemia carrier | 9 | 5 | 14 |
| Probable beta thalassaemia carrier | 1 | – | 1 |
| Alpha thalassaemia | 2 | 1 | 3 |
| Hereditary persistence of fetal haemoglobin | 1 | – | 1 |
| Total | 93 | 50 | 143 |

***TABLE 13*** *Intraclass correlation coefficients by trial arm*

| | ICC (95% CI) | | |
|---|---|---|---|
| **Outcome measure** | **Standard care** | **Primary care parallel** | **Primary care sequential** |
| Uptake of screening test before 70 days' gestation | 0.038 (0 to 0.097) | 0.061 (0 to 0.137) | 0.142 (0.010 to 0.275) |
| Uptake of screening before 182 days' gestation | 0.053 (0 to 0.127) | 0.034 (0 to 0.081) | 0.030 (0 to 0.073) |
| Offer of screening test before 70 days' gestation | 0 (0 to 0.100) | 0.100 (0 to 0.211) | 0.135 (0.008 to 0.262) |
| Time from pregnancy confirmation to screening | 0.188 (0 to 0.376) | 0.087 (0 to 0.191) | 0.239 (0.047 to 0.431) |
| Gestational age at screening | 0.181 (0 to 0.365) | 0.063 (0 to 0.142) | 0.163 (0.014 to 0.312) |

mothers under 24 years of age generally show about 6% lower uptake of screening in the first 10 weeks of pregnancy, and SCT test uptake is about 10 days later than for mothers aged over 32 years.

## Primary outcome: uptake of screening by mother by 70 days' (10 weeks') gestation

The trial shows that rates of early antenatal SCT screening can be increased if screening is offered at the pregnancy-confirmation consultation in primary care. It is important to note that the early offer of screening affected the gestational age at which screening took place but did not significantly impact on overall uptake rates with about one in five women not having the test by 26 weeks in all three groups.

The impact of the intervention in the current trial is limited because the majority of women did not undergo screening by 70 days' gestation. This was either because testing was not offered, the offer of testing was delayed, or when offered and accepted, the testing process was delayed, or women delayed making a decision. The proportion of women who did not undergo early screening is considerable and the reasons for the delays in screening need to be considered and addressed.

Uptake was higher, however, than in a previous study of offering antenatal SCT screening in primary care, where 35% of women had the SCT test.[26] The latter study attributed the relatively low rate of uptake to system-related failures, such as training and reminder systems. In the current trial effort was made to ensure such failures were avoided.

In order to evaluate the reliability of the data obtained in the intervention phase, data were re-abstracted for 46 women from three practices. There were exact agreement for 46 cases for date of birth data; there was exact agreement for 46 cases for whether SCT testing was performed and date of test; there was 1/46 (2%) discrepancy for date of LMP, with a difference of 1 day for the discrepant dates; there were 2/46 (4%) discrepancies for date of pregnancy confirmation visit, with differences of 1 and 7 days, respectively. The intervention phase data were therefore considered to be highly reliable.

## Secondary outcomes

### *Offer of screening*

In both intervention groups, more women were offered SCT screening tests before 70 days' gestation than in the standard care group. However, more than half of the women were not offered the test at the pregnancy-confirmation consultation in primary care. GPs attributed the failure to offer screening to lack of time, language barriers or lack of training.[48,49] Ensuring that training is provided for all GPs and that translation services are available in primary care will address some of this shortfall. Lack of time suggests that GPs consider this screening test to be a lower priority than other tasks that they need to perform. If this is the case, there is a need for more discussion regarding priorities in primary care and how to address the multiple demands placed on GPs.

### *Time between pregnancy confirmation visit and screening*

When the test was offered, the organisation of phlebotomy services in primary care did not always allow same-day testing or even a day or two later.

Developments in testing may allow the use of blood spots, as in newborn screening,[50] thus reducing delays arising from inadequate phlebotomy services. However, delivery of the existing service needs to be improved to achieve a more efficient service in the interim period.

### *Mean gestational age at screening*

The results suggest that the intervention was effective at increasing the proportion of women screened early in pregnancy. However, only a minority of women who confirmed pregnancy before 10 weeks were also tested before 10 weeks' gestation. This is outside current NICE guidelines, which recommend offering testing by 8–10 weeks in order to complete PND by 12 weeks' gestation.[23] Thus although training was effective at increasing early uptake of screening, additional interventions may be needed to ensure optimal screening performance.

### *Uptake of father screening*

Fewer than 5% of fathers who were offered screening underwent testing. This is in contrast with the 90% uptake of father carrier testing for CF that was observed in a similar trial in primary care.[51] There are differences between the trials, which may account for the results: SCT screening was offered to the biological father, whereas CF screening was offered to the women's partner; and SCT screening required blood testing, whereas CF screening required a salivary sample. The regulatory environment has changed since the Hartley study,[51] such that acknowledging paternity can now be associated with enforced child support.

Limited test uptake may be explained by high levels of social and material deprivation in the trial area. The trial took place in two inner-city PCTs, which are ranked among the most deprived boroughs in England (6th and 13th out of 354 boroughs), with a high proportion of ethnic minority groups (40% of the population). High levels of social mobility and family fragmentation are associated with poverty and could explain why biological fathers do not undergo testing in this area.

Low test uptake may be further explained if biological fathers are not registered at the same practice as the mothers, thus increasing the practical difficulties of offering testing to fathers.

### *Knowledge of couple carrier status*

Increasing the proportion of women who are screened before 70 days' gestation does not facilitate reproductive decision-making if couple carrier status is not known in time for consideration of PND or termination of pregnancy. Further work is needed to identify limiting factors and improve early knowledge of couple carrier status.

### *Strengths and limitations*

The trial design was strong: allocation to trial arms was randomised, with allocation concealment and reporting of the primary end point for all participants. A second strength is that the trial was conducted in areas with high SCT prevalence and with a diverse ethnic minority population, thus the results are likely to be applicable to areas such as inner cities across the world where SCT are prevalent.

### *Generalisability*

The outcomes were achieved under trial conditions: the offer of screening was for a limited period and the research team contacted practices on a regular basis to encourage fidelity to the protocol. It is therefore unknown what systems must be in place for a screening programme to achieve the results reported here.

Contamination between the trial arms is a possibility: for example, women in the primary-care arms could be offered testing by their community midwife. The main trial outcome, date of testing, was the earliest date of testing, irrespective of who offered testing. Methods of assessing fidelity to the trial and clinical protocols are described earlier in this chapter (see Section I: trial methods/Quality assurance). Discrepancies were discussed and resolved with participating practices.

For the statistical analysis, cluster level analyses of the practice-specific means and proportions was used in order to facilitate presentation of differences in proportions. The number of observations in these analyses was the same as the number of practices (25), providing a small number of observations for multiple regression analyses. Analyses were weighted for varying cluster size using minimum variances weights.[52] This requires estimation of the ICC (rho) for each trial group and the number of practices may not have been sufficient to provide precise estimates of 'rho'. However, there was negligible difference in estimates, and no difference in interpretation, if either unweighted analyses or analyses weighted for cluster size were used. Analyses were also performed at the individual level, using the method of GEEs, incorporating adjustments to

allow for the small number of practices. These results were consistent with the cluster level analyses. Since data for father testing and maternal carriers were sparse, exact logistic regression was used but analyses implemented using ordinary logistic regression with robust standard errors gave generally consistent results. We acknowledge that the comparison of each intervention trial arm with standard care introduces a potential question of multiplicity of testing, but the results of the trial were decisive and there was negligible overall difference in women's uptake of screening between the two intervention arms.

### *Potential models of care*

Offering the SCT screening test in primary care offers the potential for earlier PND of 'at-risk' pregnancies if women who want testing take up the test at time of offer and carrier couple status is confirmed promptly. Offering antenatal SCT screening in primary care will have implications for other aspects of antenatal care, for example where will other antenatal screening tests be offered, and who will be responsible for acting on results? If there is any change to the delivery of antenatal care (i.e. offering screening in primary care or introduction of fetal DNA testing) then roles and responsibilities will need to be clearly defined. Additional problems of coordination, communication and information sharing may emerge for pregnant women and service providers if antenatal care is fragmented between primary and secondary care.

The cost-effectiveness, acceptability and feasibility of offering antenatal SCT screening in primary care are next considered: Chapter 5 – cost-effectiveness and modelling; Chapter 6 – informed Choice; Chapter 7 – acceptability to women; and Chapter 8 – feasibility in primary care.

# Chapter 5

# Cost-effectiveness of offering screening in primary care and modelling

## Introduction

The objective of the economic evaluation was to model the cost-effectiveness of the three different patterns of screening, in part using data generated by the trial. The screening approaches investigated mirror the three trial arms: Group 1 (primary care parallel), Group Two (primary care sequential) and Group 3 (standard care sequential). The economic analysis sought to predict the costs associated with the three strategies and their outcomes in terms of uptake of earlier screening, and rates of downstream events such as PND, termination of affected pregnancies (TOP), affected births, and unexpected affected births.

There is no extensive literature on the cost-effectiveness of antenatal SCT carrier screening. A recent review is presented in Karnon *et al.* (2007)[53] where four studies were identified: two small empirical studies that focus just on cost issues,[54,55] and two model-based analyses.[9,56] The two modelling studies have adopted similar structures in terms of the pathways of the decision problem. However, different modelling frameworks have been applied: Zeuner *et al.* (1999)[9] used a conventional decision tree model, and Gallivan *et al.* (2003)[56] used a mathematical modelling approach. Further, the Gallivan *et al.* report is of a feasibility study, whereas the Zeuner *et al.* model has been more fully developed in that it has been validated by comparing outputs from the model against recorded UK data for key model predictions such as PND rates. The Zeuner *et al.* model also explicitly considers the ethnic mix of the screened population and the probability of both the mother and father carrying one of the six significant SCT traits, or of being a non-carrier. The model predicts outcomes from the antenatal process such as PND, TOP, affected births and unaffected births. On the basis of its appropriateness to the decision problem being addressed by the SHIFT study and its demonstrated model validity, the Zeuner *et al.* screening model has been used as the basis of the work undertaken in this project and is described more fully later in the chapter.

The cost-effectiveness model used in this work required estimates of the proportion of women screened by trial arm and gestational age. The first section of this chapter describes the analyses and results associated with deriving such estimates. The remainder of the chapter then describes the methods and results for the cost-effectiveness work, making use of the predicted proportions of women screened.

## Methods to derive time-to-screening inputs for the CEA

Estimates of proportion of women screened by trial arm and gestational age based on the trial data were used as inputs to the cost-effectiveness analysis (CEA). These proportions were modelled from the time from LMP to screening date using a time-to-event framework. It was decided to use Bayesian–Markov chain Monte Carlo (MCMC) methods implemented in WINBUGS 1.4.3.[57] MCMC draws samples from the joint posterior parameter distribution and not only has a simulation format compatible with probabilistic cost-effectiveness analysis,[58] but also preserves the complex correlation structure between parameters, which is essential for appropriate propagation of uncertainty. This approach can readily take clustering, including clusters of different sizes, into account by including practice cluster as a 'random effect' within a hierarchical model, while at the same time providing a uniform analysis of proportion screened at any gestational age.

Based on preliminary analyses, and on the shape of the Kaplan–Meier survival curves of time to screening unadjusted for clustering (*Figure 5*), it was clear that conventional proportional hazards models did not fit the data because of the time dependency of the relative intervention effects. Based on these exploratory analyses, separate 'baseline' survival curves were fitted to each of the three trial groups, with covariates and cluster

effects included on the assumption of proportional hazards.

Time from LMP to carrier testing was modelled as a Poisson counting process, one of several ways of parameterising Cox regression in a Bayesian framework. The model defines the hazard of an individual $i$ with covariates $Z_i$ in GP practice $j$ in treatment group $G$ with covariate vector $Z_i$ at time $t$ as:

$$\lambda_{ijG}(t)=Y_{it}\lambda_{0G}(t)\exp(\beta Z_i+\gamma_j)$$

where $\beta$ is a vector of covariates, and $\gamma_j$ are GP practice effects. The cumulative hazard is then defined as $\Lambda_{0ijG}(t)=\int_0\lambda_{0ijG}(u)du$.

In the counting-process formulation the data are in the form $dN_i(t) = 1$ if individual $i$ 'fails' (is tested) at time $t$, and 0 otherwise, and $Y_i(t) = 1$ if $i$ is under observation (at risk of being tested) at $t$, 0 otherwise. With time in finely divided intervals, the data likelihood is a step function at each observation point. We can closely approximate the continuous time process with observations occurring at discrete time points, and from here we use subscripts for $t$.

$dN_{it}$ is Poisson distributed, with an expectation equal to the increment, $d\Lambda_{0t}$, in the cumulative hazard function at time $t$:

$$dN_{it}\sim\text{Poisson}(d\Lambda_{0it})$$

$$d\Lambda_{0it}=Y_{it}\,d\Lambda_{0Gt}\exp(\beta Z_i+\gamma_j)$$

where the $d\Lambda_{0Gt}$ are the step increments in the cumulative hazard for treatment group $G$. The regression coefficients $\beta$ are given vague priors N $(0, 100^2)$, and the practice effects are assumed to be drawn from a common distribution of effects on the log-hazard scale, $\gamma_j\sim N(0,\sigma_c^2)$.The between-practice precision $1/\sigma_c^2$ was given a vague Gamma (0.1, 0.1) prior. Finally, the increments $d_{\_0Gt}$ are given vague Gamma (0.1, 0.1) priors. The priors are designed throughout with the purpose of ensuring that all the posterior distributions would be dominated by the data rather than prior belief.

Note that the model specifies *separate* 'baseline' hazard functions for each treatment group. No proportional hazards assumption is being made regarding relative treatment effects. Covariate and GP practice 'cluster' effects are, however, based on proportional hazards assumptions.

The key output from the analysis is the cumulative proportion screened at time $t$, with treatment $G$, for woman in a 'new' GP practice having a practice effect $\gamma_{new}\sim N(0,\sigma_c^2)$ drawn from the estimated distribution of cluster effects, and with covariates set at their mean values $\bar{Z}$ in the trial sample:

$$S_{Gt}=1-\exp(-\Lambda_{0Gt}^{\exp(\beta\bar{Z}+\gamma_{new})})$$

A related approach to variation due to cluster effects in policy models at local and national levels is suggested by Welton *et al.*[67] (in press). These 'survival' functions were used in the CEA. We also use the number of MCMC samples in which the proportion screened at time $t$ in the primary care groups exceeds the proportion screened in the secondary care group, to construct a Bayesian '*p*-value' for differences between treatment effects.

The covariates included in the analysis were: parity (0, > 0), age group (< 24 years, 24–28 years, 28–33 years, > 33 years), and ethnicity (North European, South or South East Asian, African or African Caribbean, South European, Other, Mixed or Not known). It was decided not to control for cluster level variables because there was no evidence that randomisation had failed to achieve a balanced allocation.

Convergence of the MCMC chain was assessed by setting different starting values. Convergence appeared satisfactory by 1000 iterations. In the analyses reported the first 3000 samples were discarded, and posterior summaries were based on the next 7000 samples.

## Results from the Bayesian survival analysis

The posterior mean proportions screened in each group, adjusted for covariates and clustering, is shown in *Figure 7*. The results are shown in *Table 14*, along with posterior mean differences between the secondary care group and each of the primary care groups. The results show a close agreement between the crude proportion screened and the estimates derived from the WINBUGS analysis. The proportion screened was considerably greater in the primary care groups. At 10 weeks' gestational age, the per cent screened was 22.8% higher in the parallel testing group, and 26.3% higher in the sequential group. The difference was statistically significant at 6, 10, 14 and 18 weeks.

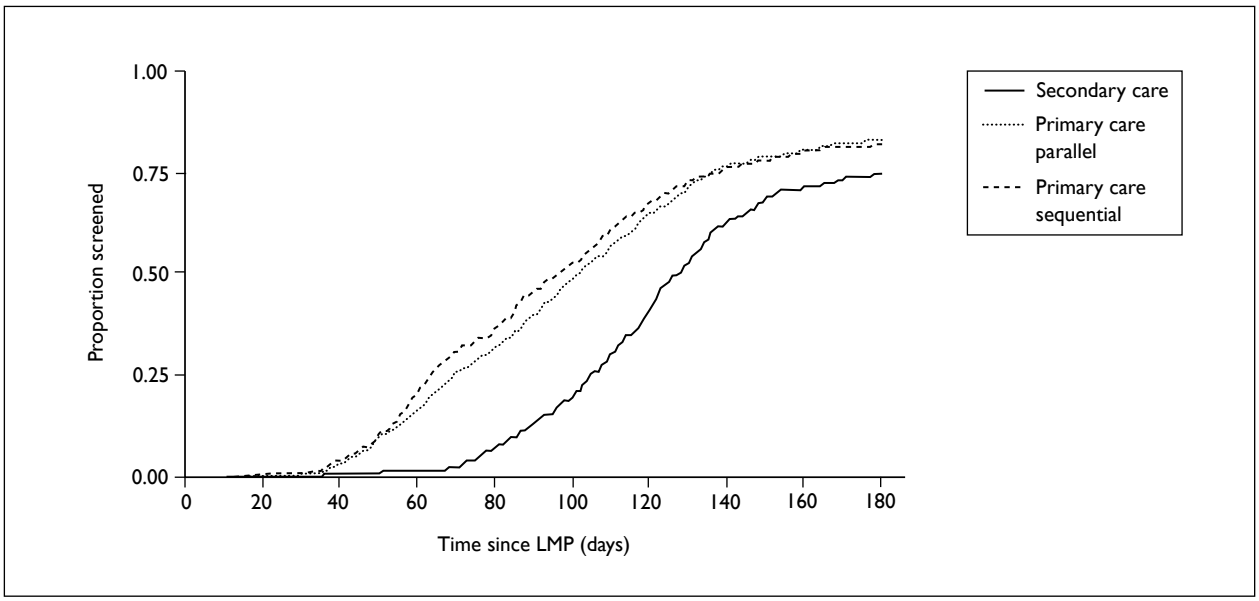



***FIGURE 7*** *Predicted proportion of women screened by group, adjusted for covariates and clustering.*

There were covariate effects on the probability of being screened (*Table 15*). Older women were more likely to be screened earlier, but multiparous women were less likely. Women belonging to the 'Not known' ethnicity group were slightly more likely to be screened later.

There were extreme levels of variation between GP practices (*Figure 8*). The caterpillar plot shows that for each intervention arm, practice effects are randomly scattered around the baseline hazard. The between-cluster standard deviation on the log-hazard scale was 0.32, with 95% CI 0.22 to 0.47. On this basis, we would expect 95% of GP practices to have hazard ratios between 1.9 times greater and 1.9 times less than the median. Therefore, if the median level of screening by 10 weeks was 2.5%, 24.6% and 28.1% in the three groups as estimated in *Table 15*, we would expect screening rates to be between 0%, 8.8%, and 11.5% on each of the intervention, respectively, in a practice at the low-screening-rate extreme, and 13%, 40%, and 43%, respectively, in a practice at the high-screening-rate extreme.

## Methods for the CEA

A cost-effectiveness framework has been used, encompassing both estimation and prediction of the costs and effects associated with the three models of care. The focus is the prenatal period, so only costs and outcome measures associated with screening and prenatal care have been included. The trial has been used as the data source for events up to the screening outcome, with data from other sources used for events post screening, such as PND and termination of pregnancy.

A key outcome in the economic analysis is the proportion of women screened before 70 days' gestation, based on the trial results. Given that the trial found no gains associated with primary care screening in terms of 'informed choice' (as described in Chapter 6), this outcome was not included in the economic analysis. Using the model-based analysis, the economic evaluation has extrapolated beyond the trial to consider the longer-term process indicators, such as uptake of PND and TOP, and outcomes of affected live births and unexpected affected live births.

An incremental analysis is adopted, the increment being the difference in costs and effects between trial arms. Secondary sequential is assumed to be 'standard practice' and hence the default comparator. The alternative screening policies are compared in terms of the following incremental cost-effectiveness ratios (ICERs):

- additional cost per extra woman screened before 70 days' gestation
- additional cost per extra PND undertaken
- additional cost per extra unexpected affected live birth prevented.

## Perspective, scope and time horizon

The perspective of the study indicates the breadth of coverage in terms of cost issues and

***TABLE 14*** *Proportion screened in the three intervention groups*

| Gestational age (weeks) | Standard care | | Primary care parallel | | Primary care sequential | | Difference | Difference |
|---|---|---|---|---|---|---|---|---|
| | Observed | Estimated | Observed | Estimated | Observed | Estimated | Primary care parallel – standard care | Primary care sequential – standard care |
| 6 | 0.6 | 0.6<br>0–1.4 | 2.8 | 3.4<br>2.0–5.3 | 3.79 | 4.0<br>2.5–6.0 | 3.0<br>0.9–6.6<br>$p=0.012$ | 3.7<br>1.3–7.8<br>$p<0.0002$ |
| 10 | 2.4 | 2.5<br>1.2–4.4 | 24.3 | 24.6<br>18.7–31.9 | 28.5 | 28.1<br>21.8–34.9 | 22.8<br>11.0–40.1<br>$p<0.0002$ | 26.3<br>13.2–44.6<br>$p<0.0002$ |
| 14 | 18.2 | 18.0<br>13.2–23.9 | 46.3 | 46.4<br>37.2–56.7 | 48.8 | 48.7<br>40.0–57.8 | 28.4<br>14.2–44.6<br>$p<0.0002$ | 30.6<br>16.3–46.2<br>$p<0.0002$ |
| 18 | 49.5 | 50.0<br>40.3–60.6 | 67.6 | 68.7<br>58.5–78.9 | 69.1 | 69.4<br>59.8–78.5 | 17.9<br>3.5–32.2<br>$p=0.01$ | 18.5<br>4.6–31 3<br>$p=0.008$ |
| 22 | 71.8 | 72.8<br>62.5–82.5 | 79.6 | 80.8<br>71.6–89.2 | 77.9 | 78.4<br>69.2–86.4 | 7.4<br>–5.1 to 21.4<br>$p=0.17$ | 5.2<br>–7.4 to 17.8<br>$p=0.4$ |
| 26 | 76.5 | 77.4<br>67.4–86.3 | 83.4 | 84.7<br>76.0–92.1 | 82.4 | 82.1<br>73.5–89.5 | 6.8<br>–4.8 to 21.2<br>$p=0.17$ | 4.4<br>–7.5 to 16.7<br>$p=0.4$ |

Observed unadjusted results compared to posterior means and 95% credible intervals from the survival analysis, and difference between standard care and each of the primary care groups, with probabilities that the differences are greater than zero.

***TABLE 15*** *Risk of being screened: posterior medians and 95% credible intervals for hazard ratios for age, parity, ethnic status*

| | | 95% Interval | |
|---|---|---|---|
| | **Median** | **2.5%** | **97.5%** |
| ***Age groups*** | | | |
| < 24 years (ref.) | 1 | | |
| 24–28 years | 1.113 | 0.955 | 1.307 |
| 28–33 years | 1.208 | 1.027 | 1.409 |
| > 33 years | 1.201 | 1.027 | 1.416 |
| Parity | | | |
| 0 (ref.) | 1 | | |
| > 0 | 0.847 | 0.757 | 0.947 |
| ***Ethnic status*** | | | |
| North European (ref.) | 1 | | |
| South or South East Asian | 1.152 | 0.954 | 1.396 |
| African or African Caribbean | 1.105 | 0.927 | 1.322 |
| South European and Other European | 1.027 | 0.847 | 1.242 |
| Other | 0.984 | 0.708 | 1.330 |
| Mixed | 1.246 | 0.834 | 1.818 |
| Not known | 0.774 | 0.628 | 0.947 |

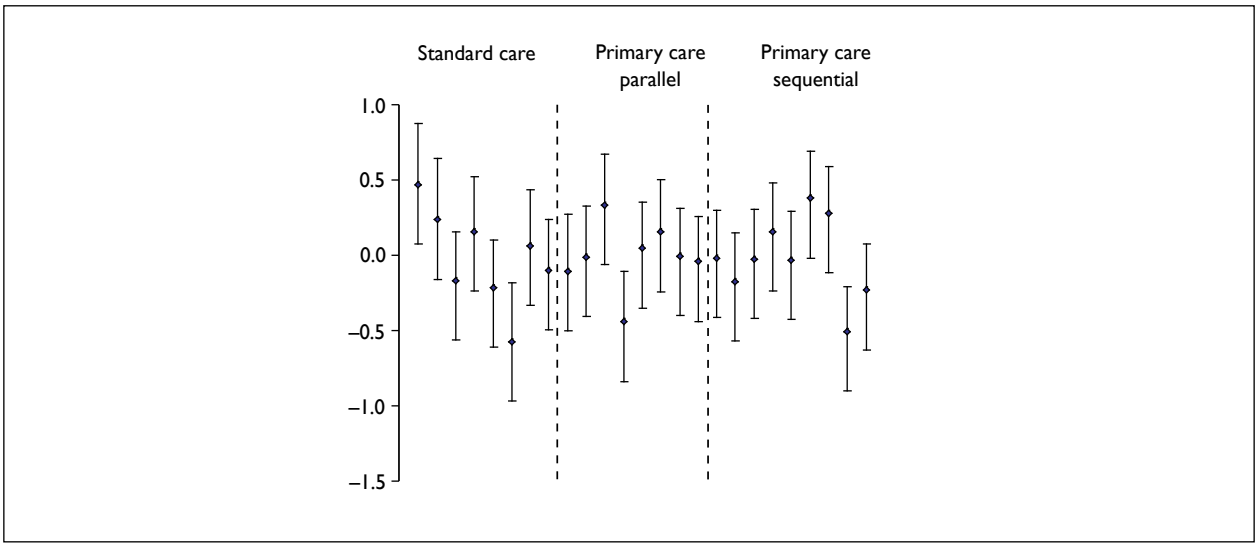



***FIGURE 8*** *Caterpillar plots showing the scatter of practice effects (95% CI) around the baseline hazard.*

is particularly important when the costs and savings might be experienced by different sectors of the economy, for example the health sector, social services and families. If the use of testing in primary care leads to earlier and greater uptake of screening, there will be cost implications for the health-care sector and for the screened women. In addition, parallel testing of partners in primary care will have cost implications. This is because the partner is being tested before the result of the woman's test is known and the woman may not be a carrier. Therefore, the economic evaluation has adopted a broad perspective and considered costs falling both on the NHS and on service users.

The base-case analysis adopted a health-sector perspective, with service-user costs additionally considered as part of the sensitivity analysis.

The scope of a study determines how extensive is the consideration of the consequences resulting from the programmes being evaluated. The time horizon of the analysis covers pregnancies to their conclusion, i.e. birth, termination or other pregnancy loss unrelated to screening. It does not include the potential effects of the screening cycle on future pregnancies.

## The model – an overview

The trial work provides new data on whether the screening alternatives are associated with differences in three outcomes: the time from LMP to screening; the proportion of women screened by 70 days; and the proportion of women making informed choices about screening. The modelling component of the project allows extrapolation beyond these observed outcomes to predict longer-term antenatal screening outcomes and comprehensive cost estimates.

The project has made use of an existing model, that reported by Zeuner *et al.* (1999)[9] (originally programmed in SAS), and the further development of that model undertaken by Karnon in his work for the National Screening Committee (programmed in EXCEL). In the model, the screening process pathways are depicted for antenatal populations described by ethnic composition, interethnic unions, the frequency of six significant SCT carrier states and the non-carrier state, and the mendelian recessive inheritance patterns. This information allows calculation of the number of homozygous, heterozygous and unaffected fetuses with their corresponding genotypes, expected each year for any given ethnic composition in the antenatal population. The second function of the model is to predict costs and effects of a screening process for an antenatal population defined by ethnic mix.

In the model runs for this project, the screening process pathways are depicted for the antenatal population observed in the trial. The model structure is based on the chronological sequence of steps during the screening process, as described in *Figure 9*. Minor modifications have been made to the model to allow for parallel screening, whereby the declared father is offered screening in advance of the result of the woman's test.

In line with the screening approaches evaluated in the trial, a universal screening strategy is modelled such that all women (with the exception of those who present too late) are eligible for screening. Not all women in the trial underwent screening and this is captured as a model parameter. While some women may have declined the offer, it is likely that others were simply not offered screening. Some of the key model assumptions are listed below.

- In the case where a woman is identified as a carrier and the father is not tested, the woman is automatically offered PND.
- The model allows for the scenario where the declared partner is not the biological father.
- Any woman presenting after the end of the second trimester (26 weeks' gestation) is too late to receive screening.
- The scenario of spontaneously miscarriage of a pregnancy is allowed for.
- The testing process is not assumed to be perfect so the model allows test results for women and partners to be false negative or false positive.
- The acceptance rates for PND and TOP are time dependent, so earlier screening can lead to higher rates.
- Prenatal diagnosis can induce miscarriage.

Thus, we have extended the Zeuner model to allow comparison of the screening approaches compared in this trial. In addition, the model has been modified in order to allow for time dependency of post-screening decisions such as PND and TOP, and also it has been adapted to allow probabilistic analyses to be undertaken.

## Cost data

The screening programme costs considered in this work are categorised as: invitation/screening, counselling through the screening and diagnosis process, laboratory testing, PND and TOP. Given the scope of the analysis, we are interested in the prenatal costs incurred by the screening programmes up to and including TOP. Costs associated with antenatal care and averted lifetime treatment costs are, therefore, not considered.

As part of the empirical work, key resource use data have been collected to estimate the short-term costs associated with the alternative approaches to screening and diagnosis of women and their partners. Data were collected prospectively on patient-specific resource use, including short-

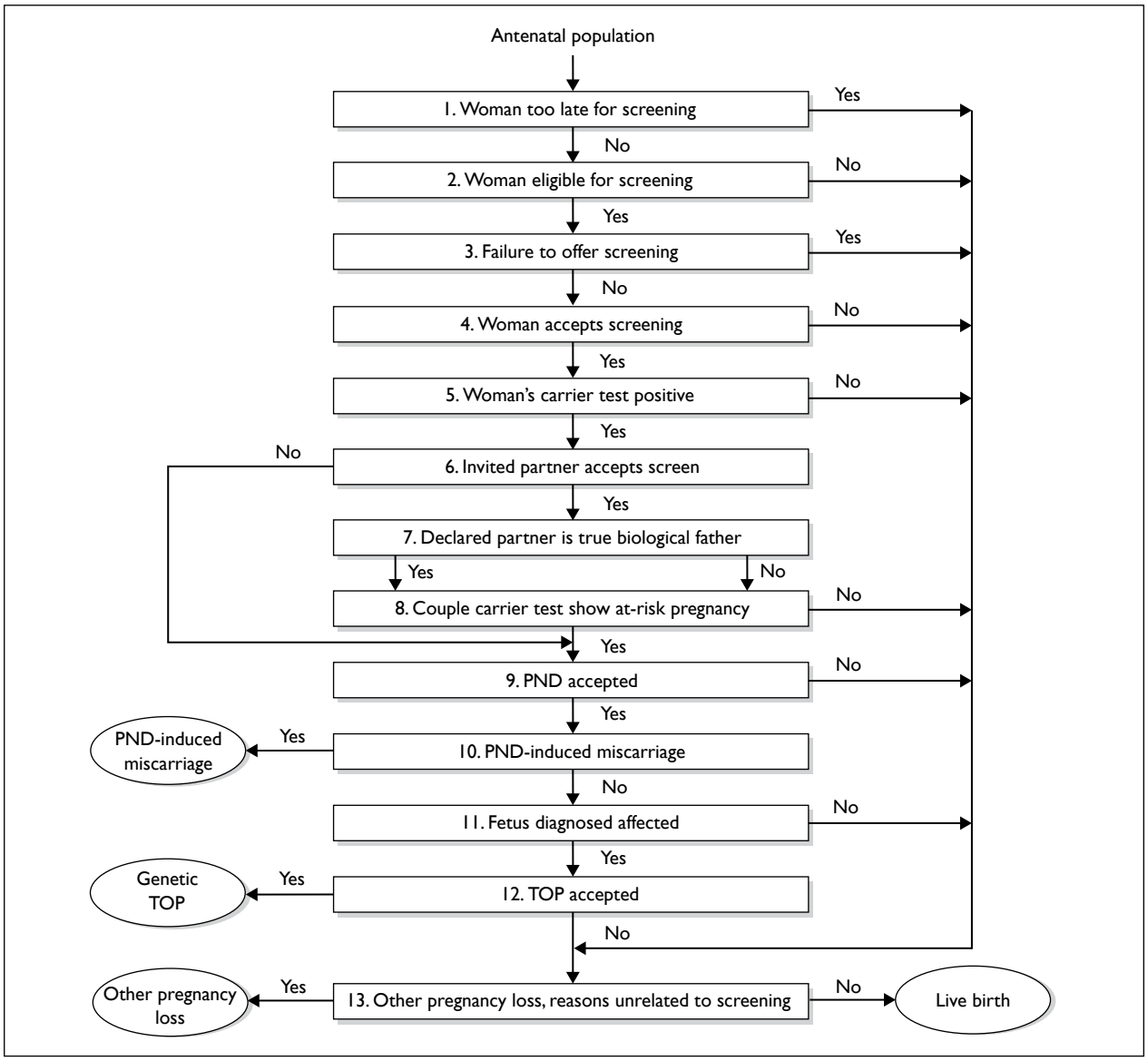



***FIGURE 9*** *Screening flow diagram.*

term events, such as screening offer; counselling carrier women, partners and couples; and diagnostic testing and subsequent procedures. These anonymous data were extracted from routine medical records of trial participants.

Data were also collected on the additional time, both for consultations and administration, associated with primary care screening, and the personnel involved. Such data came from routine practice records and from interviews with clinical personnel. Data on length of consultation were estimated for pregnant women offered testing in primary care and those offered testing in secondary care, as part of a midwifery booking appointment. Using a combination of objective and self-report data collected as part of the trial, the estimated additional length of the consultation as a result of introducing the screening test was estimated to be between 0.5 and 3 minutes, with a further 0.5 minutes if the father was present. For the base-case analysis, the assumption was made that, in the absence of a father, the additional length of this consultation was 3 minutes.

The estimated cost of a consultation in primary care, for either the sequential screening arm or the parallel screening arm varies, depending on whether the consultation is carried out by a GP or a nurse. Data on who conducted the consultation

were recorded as part of the study and so the costs were calculated based on a weighted average for the unit cost associated with the test offer. It was noted in the trial data that the majority of individuals were not tested on the same day as the offer but returned to receive the test from a phlebotomist. This use of the phlebotomist increased the cost by approximately £1.74, in addition to the cost of the test itself, estimated to be £4.00. The unit cost estimates and the main cost inputs into the model are given in *Table 16*.

The unit costs associated with laboratory tests were accessed from laboratory pricing schedules. Information on other unit costs or prices (e.g. relating to PND and TOP) were collected from relevant routine sources [e.g. Department of Health Reference Cost schedules[59] and Curtis and Netten (2006)[60] for unit cost sources for community services] and hospital finance departments in order that an overall cost per screened woman could be calculated. All costs are reported in 2006 prices.

In the acceptability component of the study, a sample of women and their partners in all arms of the trial were asked to complete a patient cost questionnaire, which aimed to record the private costs of undergoing screening (e.g. travel costs, time off work, lost income and child-care costs). Private costs for post-testing procedures, such as PND and TOP, were not collected from participants in this study for both practical and ethical reasons. Information on time taken to deliver counselling sessions was obtained through interviews with key service personnel. Other information required to estimate private costs for other procedures (such as travel modality and travel time, length of TOP procedure, etc.) were based on assumptions.

*Table 16* reports the unit cost estimates used in the economic analysis.

## Other model parameters

*Tables 17* and *18* report the model parameters describing the antenatal population studied and the screening pathways modelled. All parameters in the original Zeuner *et al.* (1999)[9] model were reviewed and a judgement made concerning the updating of the parameter value. Where new data were available from this trial, they were used. Where new data could be accessed or found in published sources for other parameters, these values were also updated. *Tables 17* and *18* detail the sources for all main parameters, with updates indicated.

For the time-to-screening variable, the model used the screening time predictions given by the WINBUGS analysis, where adjustment was introduced for clustering, parity, ethnicity, age, etc. (see *Table 20*). In line with this analysis, the cost-effectiveness work also used 3000 iterations as a burn-in phase and the next 7000 iterations to derive model inputs.

## Base-case and sensitivity analyses, and presentation of results

A base-case analysis is first presented, representing the population of women seen in the trial and using the parameter values as defined in *Tables 16–18*. The published Zeuner model was entirely deterministic so part of the project was to undertake a model development process to allow probabilistic analyses in order that parameter uncertainty might be explored.

Given the highly complex model employed in this research, for pragmatic reasons it was necessary to adopt a partial approach to the investigation of parameter uncertainty. Thus, the probabilistic analysis has focussed exclusively on parameters populated by new data from the SHIFT study. This approach serves to underplay the full level of uncertainty associated with the results and the reader needs to take this caveat into account when reviewing the analysis results. The following parameters have been varied:

- ethnic mix of the screened population
- proportion of women not screened
- probability that father is tested when the woman is a carrier
- proportions of women screened by 6, 10, 14, 18 and 22 weeks.

For the ethnic mix of the population, the sampling was from a Dirichlet distribution for the vector of probabilities for the complete set of proportions. For the not screened rates and the probability of father testing, beta distributions were used. When different values were used for different options, independent samplings were employed. For the time to screening data, the probabilistic model was populated by the iterations from the WINBUGS survival analysis. The probabilistic analyses were based on 7000 replications of the model.

***TABLE 16*** *Model cost inputs*

| Cost variable | NHS cost | Description | Sources | Private cost |
|---|---|---|---|---|
| Carrier test – woman | Secondary = £8.80<br>GP parallel = £13.51<br>GP sequential = £12.30 | Test cost is £4; GP or midwife time (3 minutes); GP arms reflect that a small proportion of women (42/677) were seen by a nurse; GP parallel arm has a slightly higher unit cost, reflecting attendance by some partners; phlebotomist cost is £1.74 | SHIFT Trial;[69] Curtis and Netten (2006)[60] | £11.47 |
| Carrier test – partner | Secondary = £5.74<br>GP parallel = £6.09<br>GP sequential = £5.74 | GP parallel arm only includes cost of additional partner tests | SHIFT Trial;[69] Curtis and Netten (2006)[60] | £11.47 |
| Carrier status counselling – woman only | £16.13 | Letter and 15-minute counselling session by midwife/counsellor | Roberts *et al.* (2007);[70] personal communication; Curtis and Netten (2006)[60] | £6.18 |
| Carrier status counselling – couple | £47.63 | Letter and 45-minute counselling session by midwife/counsellor | Roberts *et al.* (2007);[70] personal communication; Curtis and Netten (2006)[60] | £10.27 |
| PND | £343.23 | Transabdominal CVS; PND counselling; PND-induced miscarriage costs | Bricker *et al.* (2000);[71] DoH reference costs;[59] personal communication | £67.18 |
| TOP counselling | £47.25 | 45-minute counselling session by midwife/counsellor | Personal communication; Curtis and Netten (2006)[60] | £10.27 |
| TOP | £489.00 | | DoH reference costs[59] | £67.18 |

CVS, chorionic villus sampling.

***TABLE 17*** *Model parameters describing the antenatal population*

| Parameter | Description | Value/calculation | Source |
|---|---|---|---|
| Ethnic composition of the antenatal population | Probability that a woman in the antenatal population belongs to one of six ethnic groups | North European = 298/1454<br>South or South East Asian = 420/1454<br>African/ Caribbean = 357/1454<br>South European = 280/1454<br>Other = 61/1454<br>Mixed = 38/1454 | SHIFT Trial[69] |
| Interethnic unions | Probability that a woman from ethnic group *i* identifies the baby's father from group *j* | 0.0373 | Census 2001 (ONS, England)[72] |
| SCT carrier frequency by ethnic group | Probability that a woman, by ethnic group, is a carrier of one of the SCT traits or is a non-carrier | Zeuner *(Table 32)*[a] | Zeuner *et al.* (1999)[9] |
| | Probability that a declared father, by ethnic group, is a carrier of one of the SCT traits or is a non-carrier | Zeuner *(Table 32)*[a] | |
| Mendelian recessive inheritance | Probability that, if both parents are carriers of a SCT trait, the fetus inherits both traits, one trait or no trait | 0.25, 0.5, 0.25 | Zeuner *et al.* (1999)[9] |
| | Probability that, if one parent is a carrier, the fetus inherits one trait or no trait | 0.5, 0.5 | |
| Declared father's paternity | Probability that the declared father is not the biological father | 0.0370 | Bellis *et al.* (2005)[73] |

a See Appendix 4.

The base-case cost-effectiveness results have been derived from the probabilistic model analyses and so outputs represent mean values. Results have been presented using ICERs and scatters of points on the cost-effectiveness plane reflecting uncertainty in the results. The scatters contain 7000 points, each point representing one of 7000 estimates of incremental costs and effects generated by each model run. (Note: 7000 iterations were available from the WINBUGS analysis and so consistency was maintained in the probabilistic component of the CEA. This is a much larger number of samples than is commonly seen in probabilistic sensitivity analyses.)

Sensitivity analysis allows exploration of the robustness of the base-case results to plausible variations in key assumptions. Two sensitivity analyses have been undertaken. First, the perspective has been broadened beyond the health sector in order to include, additionally, costs falling on service users. Second, the uptake of PND was varied because the levels of uptake seen in the trial, albeit based on small numbers, were considerably lower than the levels assumed in the base-case run of the model. Given the length of time to run the model probabilistically, these sensitivity analyses were undertaken using deterministic model runs.

# Results

## Base-case analysis

The base-case results from the probabilistic analyses are reported in *Table 19*. For convenience and ease of interpretation, all figures are expressed as a rate per 10,000 pregnancies. Where results derive from the probabilistic analyses, 95% credible intervals are additionally reported, which simply represent the range (from 2.5% to 97.5%) of the distribution of outputs from the probabilistic model runs. Results from baseline probabilistic and deterministic analyses are very similar and so deterministic analysis results are reported for sensitivity analyses.

The transfer of screening into a primary care setting is associated with an increase in costs to the NHS of between £31,000 and £52,000 per 10,000 pregnancies, depending on the screening approach

***TABLE 18*** *Model parameters describing the model pathways*

| Parameter | Description | Value/calculation | Source |
|---|---|---|---|
| Woman too late for screening | Probability that a woman books at >26 weeks' gestation | Zeuner (*Table 14*)[a] | Zeuner *et al.* (1999)[9] |
| Failure to screen eligible women | Probability that a woman who is eligible for screening is not screened, by trial arm | Secondary = 117/441<br>GP parallel = 106/677<br>GP sequential = 109/590 | SHIFT Trial[69] |
| Time to screen | For women who are screened, time from LMP to screen, by trial arm | Trial data (see *Figure 2*) and WINBUGS predictions | SHIFT Trial[69] |
| Woman's carrier test positive | Probability that the carrier test result of a true maternal carrier is positive (1 – false-negative rate) | 0.999 | Zeuner *et al.* (1999)[9] |
| | Probability that the carrier test result of a true maternal non-carrier is positive (false-positive rate) | 0 | |
| Declared father accepts screening | Probability that the declared father is tested when maternal result is positive, by trial arm | Secondary = 10/20<br>GP parallel = 20/47<br>GP sequential = 14/24 | SHIFT Trial[69] |
| | Probability that the declared father is tested when maternal result is negative (GP parallel arm only) | GP parallel = 32/524 | |
| Couple carrier tests show at-risk pregnancy | Probability of positive couple carrier test result for a true at-risk pregnancy (1 – false-negative rate) | 0.999 | Zeuner *et al.* (1999)[9] |
| | Probability of positive couple carrier test result for a true non-risk pregnancy (false-positive rate) | 0 | |
| | Probability of positive carrier test result for a true maternal non-carrier, without a partner test result (false-positive rate) | 0 | |
| Woman accepts PND | Probability that a woman offered PND accepts the offer | Zeuner (*Table 34*)[a] | Zeuner *et al.* (1999)[9] |
| PND-induced miscarriage | Probability that a woman who has accepted PND has a miscarriage due to the procedure | 0.015 | Zeuner *et al.* (1999)[9] |
| Fetus diagnosed as affected | Probability that a truly affected fetus is diagnosed as affected (1 – false-negative rate) | 0.9925 | Zeuner *et al.* (1999)[9] |
| | Probability that a truly not affected fetus is diagnosed as affected (false-positive rate) | 0.001 | |
| Woman accepts TOP | Probability that a woman with a fetus diagnosed with thalassaemia accepts TOP | 0.95 | Zeuner *et al.* (1999)[9] |
| | Probability that a woman with a fetus diagnosed SCD accepts TOP | 0.70 | |
| Failure of fetus to reach term | Probability that pregnancy does not reach term for reasons unrelated to screening | 0.14 | HTA (and Slattery and Morrison, 2002)[74] |

SCD, sickle cell disease.
a See Appendix 4.

considered. However, this increased expenditure is matched by a large increase in effectiveness measured by the number of women screened by 70 days' gestation. Whilst the increase in screening rates by 70 days is dramatic, it still leaves the vast majority of women (i.e. over 70%) not screened by the 10-week deadline. The predictions from the model for process measures and outcomes not collected in the trial, such as PND rates, TOP rates and affected births, are also reported in

***TABLE 19*** *Base-case results – model predictions per 10,000 pregnancies (point estimates and 95% credible intervals)*

| | Standard sequential | Primary care parallel | Primary care sequential |
|---|---|---|---|
| Health sector costs | £133,469 (£109,906 to £153,720) | £185,265 (£155,382 to £206,757) | £164,086 (£136,635 to £186,850) |
| Women screened by 70 days | 264 (92 to 580) | 2556 (1276 to 4444) | 2887 (1509 to 4930) |
| Blood samples with positive result (woman) | 737 (645 to 816) | 780 (685 to 852) | 772 (677 to 851) |
| Blood samples with positive result (partner) | 61 (34 to 89) | 56 (36 to 76) | 75 (49 to 102) |
| PNDs undertaken | 50 (40 to 61) | 57 (48 to 66) | 50 (41 to 60) |
| PND-induced miscarriages | 0.75 (0.60 to 0.92) | 0.86 (0.72 to 0.98) | 0.75 (0.61 to 0.91) |
| PND result (any positive) | 4.68 (3.65 to 5.67) | 4.84 (3.96 to 5.76) | 5.62 (4.50 to 6.80) |
| PND result (SCD positive) | 2.45 (1.93 to 2.94) | 2.79 (2.21 to 3.36) | 3.01 (2.34 to 3.72) |
| TOPs undertaken | 3.82 (2.94 to 4.68) | 3.88 (3.17 to 4.61) | 4.56 (3.63 to 5.53) |
| Total births | 8595.52 (8594.77 to 8596.31) | 8595.44 (8594.76 to 8596.10) | 8594.89 (8594.02 to 8595.73) |
| Affected births | 27.83 (25.77 to 30.00) | 27.83 (25.79 to 29.96) | 27.17 (25.07 to 29.38) |
| Unaffected births | 8567.70 (8565.58 to 8569.71) | 8567.60 (8565.46 to 8659.63) | 8567.72 (8565.59 to 8569.75) |

**Note:** If credible intervals for the same measure under different strategies overlap, this does *not* necessarily mean that there is substantial uncertainty as to which strategy has the larger value. It is possible that there is considerable uncertainty as to the baseline value, but that one strategy consistently gives a higher value than the other. For example, there is substantial overlap between the credible intervals for costs of primary care sequential and control, but the credible interval for the difference between them is (£13,837 to £47,342), which does not cross zero.

*Table 19*. Ultimately, this process improvement in screening leads to a prediction that, on the basis of the assumptions used in constructing and populating this model, the number of PNDs, TOPs and affected births is not likely to be very different under the alternative screening scenarios.

The results for effectiveness are put alongside the cost results in *Table 20*, with results reported as incremental cost-effectiveness ratios, comparing both primary care strategies to the sequential secondary care model. The results indicate a cost-effectiveness ratio of £12 per additional woman screened by 70 days, for the move away from the Secondary Care service to a primary care sequential programme. Given the very small and uncertain differences between strategies in terms of other measures such as PND, TOP and affected births, ICERs for these outcomes are not reported.

The more costly primary care option is parallel testing but this appears not to be associated with more women being screened by 70 days and so this option, at least in terms of the short-term screening ICER (i.e. cost per woman screened by 70 days), is dominated by sequential screening in primary care. That is, in primary care, sequential screening has both a lower cost and better outcome than parallel screening.

The base-case results from the probabilistic analyses are also reported using cost-effectiveness planes given as *Figures 10* and *11*. A total of 7000 points is plotted on each scatter diagram, representing the mean incremental cost and effectiveness estimates from each of the model runs. The analyses are based on women screened by 70 days and the scatter is entirely within the north-east quadrant of the CE plane, indicating that the primary care policy appears very likely to be associated with both a higher cost and a larger number of women screened. The central points in the scatters indicate incremental costs of £52,000 (primary care parallel versus standard sequential) and £31,000 (primary care sequential versus standard sequential), in line with the cost figures reported in *Table 20*.

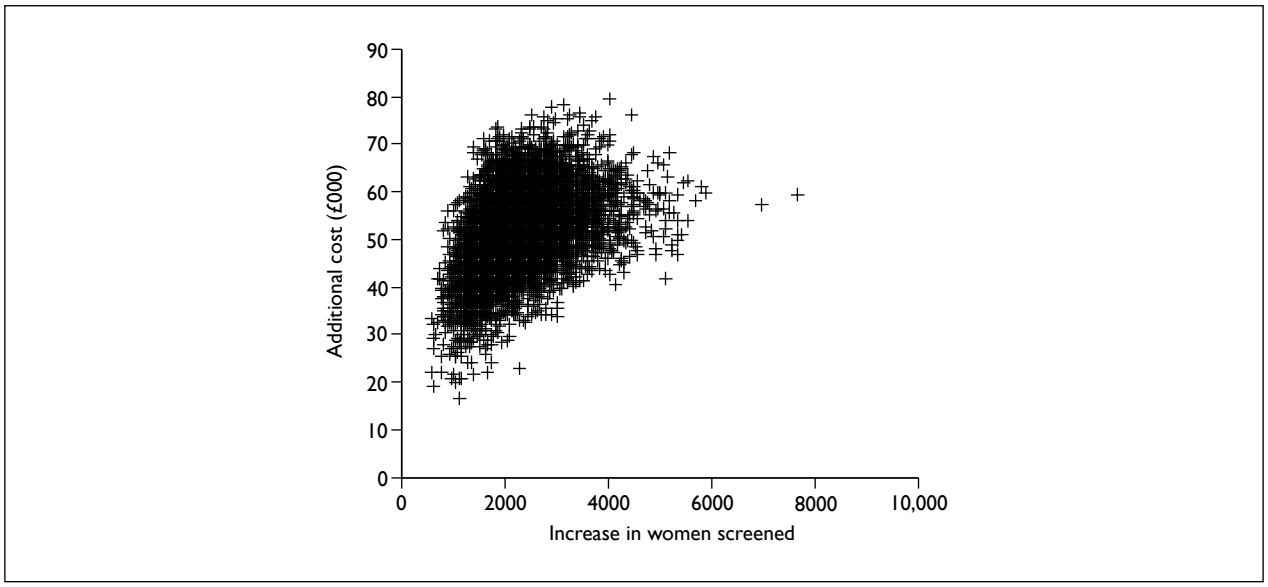
## Sensitivity analysis

The first sensitivity analysis broadened the perspective on costs, such that costs incurred by screening participants, both women and their partners, were included in addition to health sector costs. Clearly, this change will have no affect on the outcomes but does serve to inflate the cost figures considerably (by approximately 60%). The inclusion of user costs increased the cost for the standard sequential strategy to £230,385 (for a

***TABLE 20*** *Base-case ICERs*

| | Increase in cost[a] | Increase in number of women screened by 70 days[a] | ICER (woman screened 70 days)[b] |
|---|---|---|---|
| Primary care sequential vs standard sequential | £30,617 | 2623 | £12 |
| Primary care parallel vs standard sequential | £51,796 | 2292 | £23 |
| Primary care parallel vs primary care sequential | £21,179 | –331 | D |

D, dominated (i.e. primary care parallel is associated with both a higher cost and poorer outcomes).
a Rate per 10,000 women screened.
b Cost per additional woman screened by 70 days.




***FIGURES 10*** *Cost-effectiveness plane scatter diagrams.*

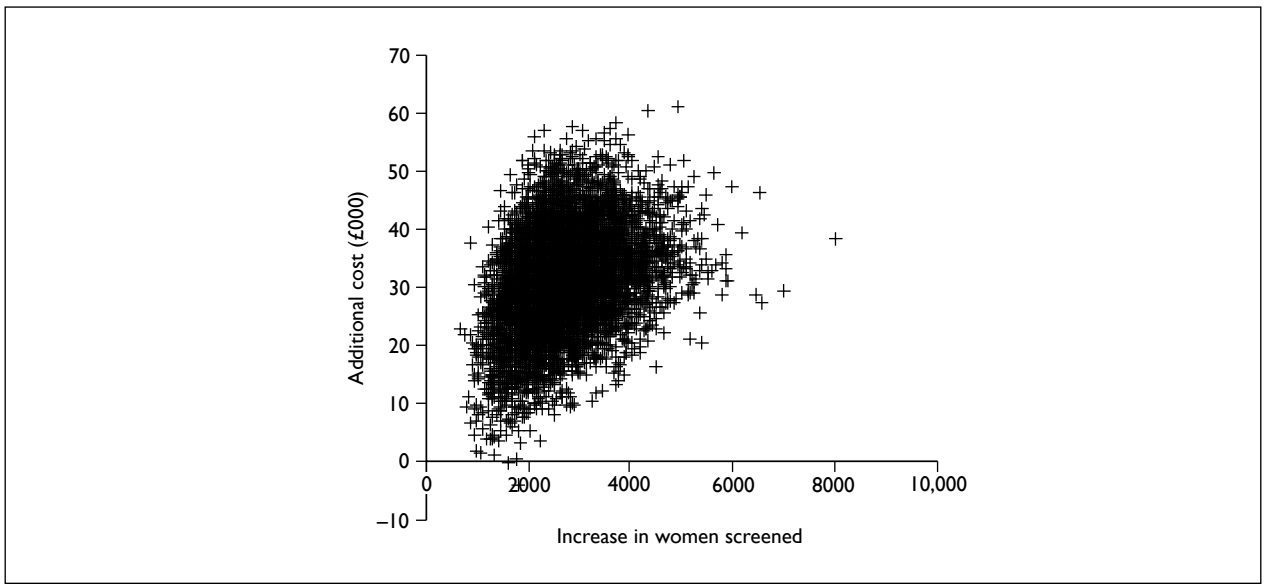



***FIGURE 11*** *Cost-effectiveness plane scatter diagrams.*

screening population of 100,000 women). The new costs for primary care parallel and primary care sequential, respectively, are then £295,983 and £266,831. The incremental analysis for this sensitivity analysis is reported in *Table 21*. Given that the incremental costs are higher than in the base case, the main ICER (comparing primary care sequential to standard sequential) has increased marginally to £14 per additional woman screened by 70 days.

The second sensitivity analysis looked at the issue of PND uptake, and ran the analyses assuming a very low PND uptake of 5% and a much higher uptake rate of 50%. The results for these analyses are reported in *Table 22*, where only health sector costs are considered. The cost predictions are as expected; costs are higher where a higher PND uptake rate is assumed, and lower where a lower rate is assumed. The numbers of women screened and the number of blood samples taken is the same as in the base-case analysis, since the only aspect changed is the assumed behaviour of women following a positive test result. Once again, as expected, a higher PND uptake rate is associated with more PNDs, more TOPs and fewer affected births. However, the incremental analyses, comparing the rates of PND and TOP and numbers of affected births between the three screening strategies, are not much affected by the assumed PND uptake rate – there remain very small and uncertain differences between the strategies on these measures of process and outcome.

## Discussion

These evaluation results indicate that the primary-care-based screening observed in the trial was associated with some improvement in screening coverage and the CEA indicates that the NHS would have to pay, on average, £12 to screen one additional pregnant woman before the 10-week threshold (using the sequential screening process). This additional cost is primarily driven by the extra time required by the GP or other HCP conducting the screening. Whilst one might be disappointed that higher levels of early screening uptake were not achieved, the cost picture suggests a rather modest sum is required in order to provide women and couples with the opportunity to make informed decisions, subsequently on further investigations and actions in relation to the pregnancy. Thus, we feel that our results lend support for a policy of primary care sequential screening in populations similar to those observed in the trial. The attractiveness of the cost-effectiveness ratios is despite the fact that over 70% of women were not screened by 10 weeks in the primary care arms of the trial. The longer-term process and outcome measures modelled as part of this work highlight the need for some caution as the suggestion is that the improved uptake of screening through primary care intervention might not be associated with increased uptake of PND or TOP, and thus may have little affect on the overall numbers of affected births.

## Strengths and weaknesses of the cost-effectiveness and modelling work

- An important caveat relating to the cost-effectiveness results concerns the paucity of data on the additional costs associated with the screening process. As part of the trial, data were collected on consultation times but these data were partial and not straightforward to analyse and interpret. Therefore, it should be recognised that if primary care screening could be undertaken without extending the consultation by the 3 minutes estimated in our analyses then, unsurprisingly, the cost-effectiveness results for such screening would look considerably more attractive.
- This work built on an existing published model, and having this as a starting point has both advantages and drawbacks. On the plus side, the model used in this work had been developed over several years, and fully reflects the complexity of the clinical context and the screening pathways. Thus, modelling some of the detail of the clinical condition was already in place and so the focus of our work was adaptation rather than modelling from scratch. Further, the model had been through an extensive validation process with comparison made of model predictions and observed screening outcomes. On the negative side, the process of familiarising ourselves with such a highly complex model was not an inconsiderable task, especially given that the model was originally built to address a different policy question.
- One of the main data inputs for the model is the time to screen by trial arm. An important strength of the work is that it is based on new data from a large randomised controlled trial. Further, these model inputs have been analysed such that they both adjust for the cluster nature

***TABLE 21*** *ICERs from the sensitivity analysis including both NHS and private costs*

| | Increase in cost[a] | Increase in number of women screened by 70 days[a] | ICER (woman screened 70 days)[b] |
|---|---|---|---|
| Primary care sequential versus standard sequential | £36,446 | 2623 | £14 |
| Primary care parallel versus standard sequential | £65,598 | 2292 | £29 |
| Primary care parallel versus Primary care sequential | £29,152 | –331 | D |

D, dominated (i.e. primary Care Parallel is associated with both a higher cost and poorer outcomes).
a Rate per 10,000 women screened.
b Cost per additional woman screened by 70 days.

***TABLE 22*** *Results from sensitivity analysis where PND uptake rate is varied*

| | Assumed PND uptake | | | | | |
|---|---|---|---|---|---|---|
| | 50% | | | 5% | | |
| | Standard sequential | Primary care parallel | Primary care sequential | Standard sequential | Primary care parallel | Primary care sequential |
| Health sector costs | £128,540 | £179,712 | £159,057 | £115,658 | £165,199 | £145,914 |
| Women screened by 70 days | 264 | 2556 | 2887 | 264 | 2556 | 2887 |
| Blood samples with positive result (woman) | 737 | 780 | 772 | 737 | 780 | 772 |
| Blood samples with positive result (partner) | 61 | 56 | 75 | 61 | 56 | 75 |
| PNDs undertaken | 37 | 42 | 37 | 3.73 | 4.25 | 3.72 |
| PND-induced miscarriages | 0.56 | 0.64 | 0.56 | 0.06 | 0.06 | 0.06 |
| PND result (any positive) | 3.48 | 3.60 | 4.18 | 0.35 | 0.36 | 0.42 |
| PND result (SCD positive) | 1.82 | 2.08 | 2.24 | 0.18 | 0.21 | 0.22 |
| TOPs undertaken | 2.84 | 2.88 | 3.39 | 0.28 | 0.29 | 0.34 |
| Total births | 8596.67 | 8596.60 | 8596.20 | 8599.67 | 8599.66 | 8599.62 |
| Affected births | 28.80 | 28.80 | 28.30 | 31.32 | 31.32 | 31.27 |
| Unaffected births | 8567.87 | 8567.81 | 8567.90 | 8568.34 | 8568.34 | 8568.35 |

of the trial and for various covariates using the WINBUGS-based analyses of the time-to-screen data.

- The modelling work has, where possible, based its inputs on new published evidence for model parameters. The project, therefore, serves to re-emphasise the realities of important gaps in knowledge relating to this clinical area. For example, data on uptake of PND and TOP in this context is very sparse, particularly when issues of variation by ethnic group and timing of screening are considered.
- Probabilistic analyses allow the importance of parameter uncertainty to be explored. The scatter diagrams reported in this chapter give an indication of the uncertainty that exists in the mean estimates of cost and effect. The work reported here represents a partial investigation of the extent of parameter uncertainty because of the exclusive focus on those parameters

where we had new data from the SHIFT Trial. Thus, the uncertainty demonstrated reflects that seen in the trial alone and is an underestimate of the full parameter uncertainty as the values on other parameters are not known with certainty.

## Some notes on choice of survival analysis methods and differences between methods

The choice of methods and comparisons between methods on the primary trial outcome deserve some comment. The GEE approach and the cluster-based method used as a sensitivity analysis produced estimates of the proportion screened, and differences between interventions in proportion screened that were comparable to the Bayesian MCMC analysis (*Table 14*) used in the CEA. The confidence intervals for the Bayesian analysis are a little wider. This is a reflection of the fact that the CEA results apply not to a cluster with an 'average' screening rate, but to a 'new' practice drawn at random from the estimated population at practices, of which the trial practices were a sample. Practices were so variable that the predicted absolute difference in per cent screened by 10 weeks between primary care and secondary care settings, while averaging about 20% (*Table 14*) might be anywhere between 10% and 30%.

With the increasing trend towards probabilistic methods, there has been a move in recent years in health technology assessment *either* to estimate treatment effects and their variances and then enter these as parameters in the CEA, *or,* to integrate the efficacy and CEAs in a single unified analysis. This latter approach, developed at Duke University[61,62] in the 1990s, has been advocated by a number of authorities,[63–66] and is now commonly seen in technology assessments undertaken for NICE. Analyses based on Bayesian posterior estimation using MCMC are ideal for this purpose, because the simulation format links seamlessly to probabilistic decision modelling. This approach is particularly useful for cluster randomised trials, where the clustering can be accommodated in a Bayesian hierarchical model within the CEA.[67,68]

Of course, a further advantage of a single integrated analysis is that it provides a coherent basis for inference and decision-making. While, in this case, treatment differences were very clear, and all forms of analysis would lead to the same conclusions, this will not always be the case.

In the SHIFT Trial, the form of data analysis that was specified in advance was the GEE analysis. However, the analytic requirements of the CEA were not fully considered at that stage. As a result, we have had to undertake, and present, two separate analyses, on the basis that the GEE analyses must be presented as it was specified in advance, but GEE was not capable of being extended to meet the requirements of the CEA.

## Future research

The separation between disciplines is giving rise to a series of related anomalies that need to be urgently addressed in methodological research. For example, standard methods for powering trials are based on efficacy alone, even when a CEA is to be run alongside the trial, as was the case in SHIFT. Sample size considerations, and data analysis methods, should take account of both the need for sound statistical inference and cost-effectiveness.

# Chapter 6

# Impact on informed choice of offering antenatal SCT screening in primary care

The secondary outcome measures of the trial aim to determine the effectiveness, acceptability and feasibility of offering antenatal SCT screening at the pregnancy-confirmation consultation in primary care. This chapter discusses informed choice as a measure of effectiveness.

## Informed choice

As with other screening programmes, a central aim of the NHS SC&T Screening Programme is to offer couples the opportunity to make an informed choice about participation in the screening programme. Research on the factors associated with informed choice for people making health-care decisions has tended to assess one dimension only, most often knowledge about a procedure. It is now widely acknowledged that informed choice is more complex than this and involves several dimensions. A consensus is emerging that informed choices have two core characteristics: first, they reflect an individual's values, and second, they are made in the context of good knowledge. Building on this, we have developed, to our knowledge, the first operational definition of an informed choice: *'a decision based on relevant knowledge, consistent with the decision-maker's values and behaviourally implemented'*.

Thus, an informed choice to accept testing is one based on good knowledge, where those with positive attitudes towards undergoing the test have it; an informed choice to decline testing is one based on good knowledge where those with negative attitudes towards undergoing the test do not have it. Choices based on poor knowledge, or which are inconsistent with values, are classified as uninformed.

## Lack of informed choice in the context of screening for SCT

Many factors have been identified as important in limiting the opportunity for couples to make informed choices in the context of antenatal screening for SCT. They include:

- failure to offer screening or screening offered too late in pregnancy
- couples lack of knowledge about the screening test
- screening process takes too long
- diagnostic testing offered too late in pregnancy.

## Reducing delays in the screening process

Offering screening early in pregnancy has the potential to maximise both the uptake of tests and the range of reproductive choices that are available subsequently.[15,16] The earliest stage at which antenatal screening can be offered practically is at the pregnancy-confirmation consultation in primary care. However, some characteristics of GPs' primary care consultations may impede the facilitation of informed choices. The duration and context of the primary-care pregnancy-confirmation consultation is perhaps less conducive to facilitating informed choices than the booking appointment conducted by a midwife. GPs have less time than midwives for their first consultation with a pregnant woman. Further, women booking with a midwife may have had their pregnancies confirmed several weeks earlier, and are therefore more likely to be primed to receive, retain and process information regarding antenatal care in a way that women confirming their pregnancies are less likely to be.

### Participants

In total, 464 pregnant women were offered antenatal SCT screening – 419 (90.3%) from ethnic groups at high risk for SCT. Pregnant women were eligible to complete assessments of informed choice if (1) they attended participating practices to report their pregnancy; (2) they wanted to continue their pregnancy; (3) they were less than 19 weeks 6 days' gestation at their first visit to primary care; (4) they had no written record of SCT carrier status; (5)

they had certain LMP estimates of gestation; and (6) they were aged 18 or over and they consented to take part in the trial. Women who miscarried before being contacted by the research team ($n = 40$) and to whom the test was not offered according to the study protocol ($n = 43$) were also excluded.

## Outcome measures

The questionnaires used were developed for use in populations with low levels of literacy.[75]

- *Knowledge* This 10-item scale covered the main areas deemed important in professional guidelines for informed consent for screening,[76] and made specific to screening for SCT trait. The alpha coefficient of internal reliability in this sample was 0.66. Good and poor knowledge were defined by the mid-point of the scale, with scores above 5 denoting good levels of knowledge.
- *Attitudes towards undergoing the test* This scale consisted of four items, assessing the extent to which women perceive undergoing the test themselves (not the test *per se*) positively or negatively. The alpha coefficient of internal reliability in this sample was 0.70. Positive and negative attitudes were defined by the mid-point of the scale, with scores above 12

***TABLE 23*** *Demographic characteristics of women in each of the three trial arms*

| | Percentage or median (IQR) | | | |
|---|---|---|---|---|
| | **Primary care parallel (*n* = 191)** | **Primary care sequential (*n* = 158)** | **Secondary care sequential (*n* = 115)[a]** | ***p*-value** |
| Primiparae (%) | 61.3 | 57.0 | 58.3 | 0.83 |
| IMD 2004 score | 39.7 (32.3 to 49.2) | 35.9 (28.7 to 41.7) | 36.2 (31.4 to 43.9) | 0.11 |
| Highest educational qualification (%)[a] | | | | |
| No qualification | 7.9 | 8.9 | 9.6 | 0.06 |
| GCSE or similar | 15.7 | 20.9 | 22.6 | |
| GCE A level or similar | 14.1 | 16.5 | 7.0 | |
| Further education or similar | 20.9 | 17.1 | 20.9 | |
| Degree or similar | 38.7 | 35.4 | 38.3 | |
| Missing | 2.6 | 1.3 | 1.7 | |
| Age at completion of questionnaire (years)[b] | 28.2 (24.2 to 31.3) | 28.4 (25.9 to 33.2) | 30.0 (25.0 to 33.6) | 0.16 |
| Gestation at completion of questionnaire (weeks)[b] | 8 (7.0 to 11.0) | 9 (8.0 to 12.0) | 18 (16.0 to 21.0) | < 0.001 |
| Practice-reported ethnic group (%) | | | | |
| Asian | 22.0 | 48.7 | 28.7 | < 0.001 |
| African/African Caribbean | 34.6 | 15.2 | 21.7 | |
| North European | 10.0 | 6.3 | 13.9 | |
| South European | 5.2 | 3.8 | 8.7 | |
| Other | 24.1 | 20.9 | 21.7 | |
| Mixed | 2.6 | 2.5 | 3.5 | |
| Not recorded | 1.6 | 1.3 | 0.9 | |
| Other non-North European | 0.0 | 1.3 | 0.9 | |
| Questionnaire completed on telephone (%) | 88.0 | 84.2 | 84.4 | 0.71 |
| Questionnaire translated (%) | 16.2 | 27.2 | 17.4 | 0.24 |

a One case had missing values for informed choice and attitude.
b Median (interquartile range).

denoting positive attitudes towards undergoing the test.
- *Screening uptake* This was extracted from laboratory records.
- *Informed choice* Choices about antenatal SCT screening were classified as 'informed' or 'uninformed' according to women's knowledge about antenatal SCT screening, their attitudes towards undergoing screening and whether or not they underwent screening. Women with positive attitudes towards having the test (attitude score greater than 12) and good knowledge (knowledge score greater than 5), who underwent antenatal SCT screening, were classified as making an informed choice to undergo screening. Women with negative attitudes and good knowledge who did not have screening were classified as making an informed choice to decline screening. Total rates of informed choice were made by summing the number of women who made an informed choice to accept, with the number who made an informed choice to decline the screening test. Other choices were classified as 'uninformed'.

There is good evidence to support the validity of this classification.[75,77] The measure was simplified for use by a population with low levels of literacy, and was adapted for antenatal SCT screening. Evidence of the reliability and validity of the simplified measure can be found in Dormandy *et al.* (2007).[75]

## Demographic details

Women provided information of their dates of birth and gestation at the time of questionnaire completion, along with details of their highest levels of education. Information on parity and ethnicity was obtained from practices. Neighbourhood levels of deprivation data were estimated from postcodes to which the study materials were sent.[78]

## Procedure

Consent was sought from individual women to participate in the part of the trial assessing informed choice and acceptability of being offered screening in primary care. Women were verbally informed of the study and provided with leaflets by the attending HCP at their first visits to confirm their pregnancies. Women were asked to consent to their contact details being given to the research team. A female researcher contacted those agreeing to this, by telephone in the first instance, to seek consent to participate. Consenting women were invited to complete questionnaires on the telephone or by post. Up to two reminders were sent, along with a questionnaire. Women for whom English was not their preferred language were invited to complete the questionnaire in the language of their choice. Twenty languages other than English were used in telephone translations and nine languages other than English were used in written translations. About half of the women completed the questionnaire after they had provided a blood sample for testing.

The trial offered a choice of telephone or postal as methods for completion to achieve higher response rates. Telephone completion compared with postal completion allows for ready translation to more languages and provides social support to complete the questionnaire. Perhaps most importantly it removes the reading obstacle to questionnaire completion, thereby allowing the estimated 20–25% of the UK population who are functionally illiterate to participate in the research process. The procedures used to obtain a representative response rate are described in more detail in Appendix 3.

## Data analysis

Proportions and medians (IQRs) were tabulated by trial arm. *p*-Values were obtained from logistic or linear regression of the variable on trial arm, using robust standard errors to allow for clustering by practice. Logistic regression was used to estimate odds ratios and their confidence intervals for making an informed choice by trial arm. Adjustment was made for age group, parity, ethnicity, education, index of multiple deprivation (IMD) 2004 score, language (English or translated) and method (telephone or postal) of questionnaire completion. Robust standard errors were estimated to allow for clustering by general practice. Multiple linear regression was used to identify independent predictors of knowledge.

## Results

### *Response rate*

There were 993 women who agreed to be contacted by the research team. Of these women, 727 (73%) agreed to take part and 511 (70%) completed questionnaires were received. Completed questionnaires were obtained from 464 (68%) women who met the eligibility criteria for the main analysis.

***TABLE 24*** *Attitudes, knowledge, screening uptake and informed choice among women*

| | Percentage or median (IQR) (*n*) | | | | |
|---|---|---|---|---|---|
| | **Primary care parallel (*n* = 191)** | **Primary care sequential (*n* = 158)** | **Secondary care sequential (*n* = 115)** | **All (*n* = 464)[a]** | ***p*-value** |
| ***Proportion of all subjects*** | | | | | |
| Making an informed choice (%)[a] | 34.0 | 23.4 | 34.8 | 30.6 | 0.38 |
| Uninformed choice, poor knowledge (%) | 62.8 | 72.1 | 60.0 | 65.3 | 0.47 |
| Uninformed choice, attitude-behaviour inconsistent (%) | 3.1 | 4.4 | 5.2 | 4.1 | 0.75 |
| Uptake (%) | 92.7 | 91.1 | 87.0 | 90.7 | 0.45 |
| ***Attitudes*** | | | | | |
| Attitude median score (0–24, higher score = more positive attitude)[b] | 23 (20 to 24) | 23 (19 to 24) | 24 (20 to 24) | 23 (20 to 24) | 0.55 |
| Proportion with positive attitudes (%) | 96.3 | 94.3 | 96.5 | 95.7 | 0.60 |
| Proportion acting consistently with attitudes: *positive* attitude, *tested* (%, *n*/*N*) | 93.5 (172/184) | 93.3 (139/149) | 88.3 (98/111) | 92.1 (409/444) | 0.44 |
| Proportion acting consistently with attitudes: *negative* attitude, *not tested* (%, *n*/*N*) | 29 (2/7) | 44 (4/9) | 50 (2/4) | 40 (8/20) | 0.81 |
| ***Knowledge*** | | | | | |
| Knowledge median score (0–10, higher score = better knowledge) | 5 (3 to 6) | 4 (2 to 6) | 5 (3 to 6) | 4 (3 to 6) | 0.33 |
| Proportion with good knowledge (%) | 37.2 | 27.9 | 40.0 | 34.7 | 0.47 |

a One case had missing values for informed choice and attitude.
b Median (interquartile range).

### *Characteristics of the sample*

*Table 23* summarises the demographic characteristics of women in each of the three trial arms. The groups did not differ on parity, IMD 2004 score, educational level, age, method of completion or use of translated questionnaires.

Significant differences were observed in ethnicity and the gestation at which questionnaires were completed. For the primary care sequential group, 48.7% were described as Asian, in comparison with 22% in primary care parallel and 28.7% in secondary care sequential. For the primary care parallel group, 34.6% were of African/African Caribbean ethnicity, in comparison with 15.2% in primary care sequential and 21.7% in secondary care sequential. The gestation at completion of the questionnaires was 8 weeks (7–11) for primary care parallel, 9 weeks (8–12) for primary care sequential and 18 weeks (16–21) for secondary care sequential.

### *Rates of informed choice and method of test offer*

Less than one-third of women made an informed choice to accept or decline screening (30.6%) (*Table 24*). Attitudes were strongly positive towards undergoing antenatal SCT screening and did not vary by trial arm ($p = 0.55$). The proportion of women with positive attitudes was 96.3%

***TABLE 25*** *Predictors of women making an informed choice*

| | | Relative odds of making an informed choice | 95% CI | *p*-value |
|---|---|---|---|---|
| Age (years) | < 24 | 1.00 | – | |
| | 24–27.9 | 1.13 | (0.46 to 2.77) | 0.793 |
| | 28–31.9 | 2.02 | (0.96 to 4.25) | 0.063 |
| | ≥ 32 | 2.84 | (1.23 to 6.57) | 0.014 |
| | Not known | 1.04 | 0.16 to 6.84) | 0.971 |
| Parity | Multiparous | 1.0 | – | |
| | Primiparous | 1.30 | (0.81 to 2.10) | 0.282 |
| Ethnicity | Low risk | 1.00 | – | |
| | High risk | 0.50 | (0.26 to 0.93) | 0.030 |
| Education | None | 1.00 | – | |
| | GCSE/A level/further education | 6.26 | (1.25 to 31.3) | 0.025 |
| | Degree or above | 7.30 | (1.37 to 38.9) | 0.020 |
| | Not known | 11.39 | (1.62 to 80.2) | 0.015 |
| IMD 2004 score | | 0.99 | (0.97 to 1.02) | 0.648 |
| Language of QR completion | English | 1.00 | – | |
| | Translated | 0.13 | (0.05 to 0.36) | < 0.001 |
| Completion method | Postal | 1.00 | – | |
| | Telephone | 2.03 | (0.93 to 4.44) | 0.077 |
| Study group | 1 | 1.07 | (0.56 to 2.02) | 0.843 |
| | 2 | 0.67 | (0.36 to 1.25) | 0.212 |
| | 3 | 1.00 | | |

for primary care parallel, 94.3% for primary care sequential, and 96.5% for secondary care sequential.

The majority of women acted consistently with their positive attitudes towards undergoing screening, *i.e.* they underwent screening. Knowledge was low and did not vary by trial arm ($p = 0.33$). Screen uptake and rates of informed choice did not vary by trial arm ($p = 0.45$ and $p = 0.38$, respectively). The majority of choices were classified as 'uninformed' because of poor knowledge (91%), and not because woman acted inconsistently with their attitudes (20%). Women knew most about (1) options following PND and (2) sickle cell disease, and least about thalassaemia and inheritance of the conditions.

### *Predictors of making an informed choice*

Education, age, language of questionnaire completion and ethnicity were all significant predictors of making an informed choice (*Table 25*). Having a degree (OR 7.30, CI 1.37 to 38.9) or education to GCSE/A level/further education (OR 6.26, CI 1.25 to 31.3) versus no education, were the two strongest predictors of making an informed choice. Being in the oldest age category (OR 2.84, CI 1.23 to 6.55) was associated with informed choice. Having the questionnaire translated (OR 0.13, CI 0.05 to 0.36) or being from a high-risk ethnic group (OR 0.50, CI 0.26 to 0.93) predicted an uninformed choice.

### *Predictors of good knowledge*

Language of questionnaire completion, education and method of questionnaire completion were all significant predictors of knowledge (*Table 26*).

## Discussion

Being offered antenatal SCT screening in primary care at the time of pregnancy conformation did

***TABLE 26*** *Predictors of women's knowledge*

| Model | | Coefficient | 95% CI | *p*-value |
|---|---|---|---|---|
| Age (years) | < 24 | – | | |
| | 24–27.9 | 0.32 | (–0.33 to 0.98) | 0.318 |
| | 28–31.9 | 0.83 | (0.19 to 1.47) | 0.013 |
| | ≥ 32 | 0.94 | (0.23 to 1.64) | 0.011 |
| | Not known | –0.09 | (–1.87 to 1.70) | 0.919 |
| Parity | Multiparous | – | | |
| | Primiparous | –0.12 | (–0.27 to 0.51) | 0.529 |
| Risk based on ethnicity | Low SCT risk | – | – | |
| | High SCT risk | –0.51 | (–1.03 to 0.04) | 0.051 |
| Highest educational qualification | No qualification | – | | |
| | GCSE/A level/further education | 0.66 | (–0.11 to 1.42) | 0.088 |
| | Degree or above | 1.36 | (0.54 to 2.18) | 0.002 |
| | Not known | 0.90 | (–0.21 to 2.01) | 0.106 |
| IMD 2004 score | | –0.02 | (–0.04 to 0.01) | 0.116 |
| Language of questionnaire completion | English | – | | |
| | Translated | –2.10 | (–2.65 to –1.56) | 0.001 |
| Questionnaire method | Postal | – | | |
| | Telephone | 1.07 | (0.43 to 1.71) | 0.002 |
| Study group | 1 | 0.11 | (–0.43 to 0.66) | 0.667 |
| | 2 | –0.35 | (–0.81 to 0.10) | 0.120 |
| | 3 | – | | |

not undermine woman making informed choices. Women were as likely to make an informed choice when the test was offered in primary care as when it was offered by midwives later in pregnancy. However, less than one-third of women made an informed choice about screening. This is lower than has been observed in the context of other antenatal screening tests.[79–81]

Almost all uninformed choices were classified as such because of poor knowledge. The proportion of women with good knowledge in the present study was also lower than that observed in the context of antenatal Down syndrome screening.[79–81] This may be because levels of neighbourhood deprivation were greater in the current sample or because greater effort was made to include people who did not speak English and are often excluded from the research processes. Alternatively, knowledge of SCT may be poorer than knowledge of Down syndrome.

Levels of informed choice in this sample did not appear to be undermined by attitude–behaviour inconsistency, that is the great majority of women who had a positive attitude towards testing did so.

Being educated to degree level, being older and being in a low-risk ethnic group were all significant predictors of making an informed choice and of having good knowledge. Patient characteristics have been shown to predict the amount and type of information provided by HCPs, with patients from minority ethnic groups, younger patients, and patients of lower socioeconomic status being less likely to receive adequate information.[82–84] It is not possible to ascertain from the current study whether less educated, younger women from minority ethnic groups were less likely to make informed choices because of limited information provision at the point of screening offer or because of the way in which those women went on to process that information.

### *Implications for practice*

Whilst most women in this sample had positive attitudes towards antenatal SCT screening, and indeed underwent testing, a sizeable proportion

did so in the context of poor knowledge. Poor knowledge undermines informed choices and increases the likelihood of anxiety in those who are identified as carriers.[85–87] While providing written information about screening tests increases knowledge,[88] increasing knowledge in those with low levels of education is more effectively achieved if those providing information also check understanding and clarify areas not understood.[89]

### *Strengths and limitations*

This study assessed knowledge and attitudes towards undergoing antenatal SCT screening in a socioeconomically, ethnically and linguistically diverse (i.e. included women who did not speak English) sample. The study sample is representative of populations in geographical areas where antenatal SCT screening is offered routinely to all pregnant women, and as such, provides an ecologically valid estimate of the impact that screening in primary care may have on rates of informed choice. The questionnaire response rate of 66%, while good for studies in this geographical area, may have biased our results. Response rates were similar among trial arms, so it is unlikely to have biased our main comparison. Given that non-responders are likely to have poorer knowledge than responders, we have probably overestimated rates of informed choice.

While there was some evidence that training was effective as shown by the increased offer of testing from trained HCPs, the study was not powered to examine an association between individual HCPs and women making informed choices. Given there was no difference across the trial arms in rates of informed choice it is unlikely that an association would be observed between individual women and individual HCPs.

## Conclusion

Offering antenatal SCT screening in primary care, at the time of pregnancy confirmation, did not compromise woman making informed choices. Efforts to improve rates of informed choice, should focus on improving knowledge, particularly in those with low levels of education and whose first language is not English.

# Chapter 7

# Acceptability to women of offering antenatal SCT screening in primary care

The secondary outcome measures aim to determine the effectiveness, acceptability and feasibility of offering antenatal SCT screening at the pregnancy-confirmation consultation in primary care. This chapter discusses the qualitative analyses from women and emotional outcomes as measures of the acceptability to women.

## Emotional and cognitive impact of antenatal carrier detection for SCT

Antenatal SCT screening is now routinely offered in high-prevalence areas in England as part of the NHS SC&T Screening programme. One potential adverse effect of such screening is the anxiety that may accompany carrier identification. To date, only one study has described women's emotional responses to being identified as SCT carriers during pregnancy.[90] The authors concluded that screening was acceptable to women and undue anxiety was not generated. No measures appear to have been used to substantiate this observation. Six studies have formally assessed emotional responses to the antenatal detection of carriers for cystic fibrosis. Five of the six studies used standardised measures. Four reported increased levels of anxiety in women identified as carriers before learning that their partners were not carriers.[27,51,91,92] We are unaware of any studies that have assessed emotional outcomes in carrier couples or in carrier women who learn that their partners are also carriers. A 3-year follow-up study of general and antenatal populations found no increase in anxiety 3 years post testing, although carriers were less positive than non-carriers in their feelings about their test results.[93]

The present study used standardised measures of anxiety in a cohort of women participating in the SHIFT Trial (see Chapter 4) to describe the emotional and cognitive impact of identifying women as carriers of sickle cell or thalassaemia during pregnancy.

### Design

A case-controlled retrospective, descriptive design was used to compare emotional and cognitive outcomes for women receiving a carrier or a non-carrier test result following antenatal SCT screening.

### Participants

In total, 846 women were eligible for the study: 68 (8%) of these women were identified as carriers of SCT; 17 (25%) declined to take part; and 29 (42.7%) had a gestational age greater than 25 weeks when their test results were available to the research team. Of the remaining 22 carriers, 15 (68.2%) completed questionnaires. For 5 of these 15 women, carrier status information was available within the health-care system, but not to the GP at the time of test offer. Of the remaining 10 women, the couple carrier status was known by four women at the time of questionnaire completion: one was an 'at-risk couple' (i.e. the baby's father was tested and found to be a carrier) and three were 'not at-risk couples' (i.e. the babies' fathers were tested and found not to be carriers). Six women did not know their couple carrier status at the time of questionnaire completion, but one woman had been offered PND, suggesting that the carrier status of the father could not be determined in the current pregnancy.

Overall, 778 (92%) of the women tested were found not to be carriers: 74 (9.5%) of these women were matched to 22 carriers by practice and gestation when the result was available, and 40/74 (54%) completed questionnaires.

### Outcome measures

- *State anxiety* was assessed using the six-item, short-form Spielberger State-Trait Anxiety Inventory.[94]
- *Feelings about the test result* were assessed using a list of 11 adjectives.[95] Respondents were asked to select the adjectives that most applied to their feelings about their test results from the

following: surprised, happy, upset, pleased, healthy, worried, guilty, unhealthy, depressed, relieved, and indifferent. In addition to being examined individually, the five most commonly selected adjectives (happy, pleased, healthy, worried and relieved) were treated as a five-point scale assessing positive feelings about test result with higher scores, indicating more positive feelings about the test result.
- *Concern for baby's health* was assessed using a seven-point rating scale asking women how concerned they felt about their baby's health. Higher scores indicated more concern.
- *Reassurance about baby's health* was assessed using a reverse-scored seven-point rating scale asking women how reassured they felt about their baby's health. Higher scores indicated less reassurance.
- *Retrospective appraisal of decision to undergo screening* was assessed using 13 items: 10 from the Ottawa Decisional Conflict Scale,[96] which examined the extent to which women had felt uninformed and unsupported when making their decisions, and of what quality they perceived their decisions to have been, plus three items examining how satisfied they were with their decisions.

## Demographic details

Women provided details of their dates of birth, gestation at time of questionnaire completion and highest level of education. Information on parity and ethnicity was obtained from practices, and postcode deprivation data were obtained for addresses to which study materials were sent.[78]

## Procedure

Ethical approval was granted for the study (05/Q0501/36). Women were asked by the HCP to whom they reported their pregnancies if their contact details and relevant demographic information could be sent to the research team. For those agreeing, a female researcher telephoned these women to inform them further about the study and to obtain consent to take part in the evaluation, including contacting them at a later stage in pregnancy when, if they decided to be tested, their result would be available. Letters providing the same information were sent to women who could not be contacted by phone.

Test results were obtained from primary care and hospital records and consenting women who were eligible were contacted again by telephone, if possible. Women contacted by telephone were invited to complete the questionnaire ($n = 47$), using a telephone interpreter service if necessary. Women who could not be contacted by telephone or who did not wish to complete the questionnaire on the telephone were sent the questionnaire by post. A maximum of two reminders (the first by telephone with invitation to complete a questionnaire during the call, the second by post with a questionnaire enclosed) were sent to non-responders.

## Data analysis

Independent sample *t* tests were used to compare carriers and non-carriers on all outcome measures. Where *t* tests were significant, comparisons were repeated using ANCOVAs to control for age, parity and gestational age.

## Results

*Table 27* summarises the demographic characteristics of participating carriers ($n = 15$) and non-carriers ($n = 40$). The groups differed on gestation at completion of questionnaire, with carrier women completing the questionnaire significantly earlier than non-carrier women [$F(1,14) = 6.45$, $p = 0.024$].

*Table 28* presents carrier versus non-carrier comparisons on all five outcome measures. Outcomes on most measures were positive for both carriers and non-carriers. State Anxiety scores were within the population norm.[35] Carriers and non-carriers differed on only one of the five outcome measures – feelings about test results: carriers felt less positively about their test result than did non-carriers (2.67 versus 4.5, $t = -5.35$, $p < 0.001$).

*Table 29* describes which adjectives were chosen to describe feelings about test result. Carriers most frequently described feeling healthy ($n = 12$), whereas non-carriers most often described feeling pleased and happy with equal frequency ($n = 28$). No participants felt unhealthy because of their results. Worry was the most commonly chosen negative adjective for carriers ($n = 6$). Carriers also expressed surprise ($n = 4$), upset ($n = 2$), indifference ($n = 2$), guilt ($n = 1$) and depression ($n = 1$) about their test results; no non-carriers selected these adjectives.

There were insufficient numbers of carrier women to compare the anxiety scores in women who knew ($n = 4$) with those who did not know ($n = 11$) their

***TABLE 27*** *Demographic characteristics of the sample*

| | | ***n*** **(%) or median (IQR)** | | |
|---|---|---|---|---|
| | | **Carriers (*n* = 15)** | **Non-carriers (*n* = 40)** | ***p*-value** |
| Primiparae [*n* (%)][a] | | 11 (73.3) | 23 (57.5) | 0.216 |
| IMD 2004 score (higher score = more deprived)[b] | | 42.39 (38.49 to 53.92) | 40.49 (31.54 to 47.78) | 0.236 |
| Highest educational qualification [*n* (%)][a,c] | No qualification | 1 (6.7) | 2 (5.1) | |
| | GCSE or similar | 2 (13.3) | 6 (15.4) | |
| | GCE A level or similar | 2 (13.3) | 3 (7.7) | |
| | Further education or similar | 5 (33.3) | 8 (20.5) | |
| | Degree or similar | 5 (33.3) | 20 (51.3) | 0.524 |
| Age at completion of questionnaire (years)[b,c] | | 28.25 (25.83 to 29.65) | 29.01 (25.95 to 33.15) | 0.081 |
| Gestation at completion of questionnaire (weeks)[c] | | 21 (18 to 28) | 27 (20 to 32) | 0.024 |
| Ethnicity (as risk factor) [*n* (%)][a] | Non-Northern European | 15 (100) | 36 (90) | |
| | Northern European | 0 (0) | 4 (10) | 0.565 |

a chi-squared test.
b *t* test.
c Thirty-nine non-carriers.

***TABLE 28*** *Affective and cognitive outcomes of SCT carrier screening overall and by test result*

| | **Mean (SD)** | | ***p*-value** | | **Unadjusted mean difference (95% CI of difference)** |
|---|---|---|---|---|---|
| | **Carriers (*n* = 15)** | **Non-carriers (*n* = 40)** | **Adjusted[a]** | **Unadjusted** | |
| State anxiety (STAI-6)[b] | 35.71 (8.52) | 34.04 (10.43) | 0.541 | 0.624 | 1.679 (–5.51 to 8.87) |
| Feelings about test result[c] | 2.67 (1.45) | 4.5 (1.07) | < 0.001 | < 0.001 | –1.833 (–2.59 to –1.08) |
| Concern for baby's health[d] | 4.53 (2.53) | 4.25 (2.26) | 0.759 | 0.649 | 0.283 (–1.02 to 1.59) |
| Reassurance about baby's health[d] | 3.20 (2.21) | 2.87 (1.91) | 0.496 | 0.590 | 0.328 (–0.95 to 1.61) |
| Appraisal of test decision[e] | 23.93 (3.47) | 25.87 (6.31) | 0.071 | 0.078 | –1.935 (–4.12 to 0.25) |

a Covariates: age, parity, gestational age.
b *n* = 38 non-carriers, 14 carriers.
c *n* = 30 non-carriers.
d *n* = 39 non-carriers.
e *n* = 38 non-carriers.

couple carrier status at the time of questionnaire completion and of those who knew their carrier status, to compare those who knew the father was a carrier ($n = 1$) with those who knew the father was not a carrier ($n = 3$).

## Discussion

In this sample, pregnant women identified as SCT carriers during pregnancy did not experience negative emotional outcomes in comparison

***TABLE 29*** *Adjectives chosen to describe feelings about test result by carriers and non-carriers*

| | ***n* selecting adjective** | |
|---|---|---|
| | **Carriers (*n* = 15)** | **Non-carriers (*n* = 30)** |
| Healthy | 12 | 26 |
| Relieved | 9 | 24 |
| Pleased | 6 | 28 |
| Worried | 6 | 1 |
| Happy | 4 | 28 |
| Surprised | 4 | 0 |
| Upset | 2 | 0 |
| Indifferent | 2 | 0 |
| Guilty | 1 | 0 |
| Depressed | 1 | 0 |
| Unhealthy | 0 | 0 |

to non-carriers, although they did report more negative feelings about their test results. Emotional and cognitive outcomes were mainly positive, both for carriers and non-carriers, reflecting previous observations of women undergoing carrier testing for CF as well as other prenatal screening tests. There were insufficient data to compare emotional outcomes in those who knew the baby's father was a carrier with those who knew he was not a carrier or who did not know the father's carrier status. In longitudinal studies of women's emotional responses to prenatal testing, raised anxiety generally subsides after the results of diagnostic testing.[97] In the current context, none of the three carrier couples elected to proceed to prenatal diagnostic testing. Anxiety may therefore have persisted until after the birth of the child when uncertainty would have been resolved regarding the carrier status of the child. Longitudinal studies of sufficient numbers are needed to follow up carriers after their carrier status is known, to estimate more precisely the extent and nature of anxiety generated by antenatal carrier detection. This should include follow up of those who (1) opt for PND and (2) do not opt for PND, including follow-up until after the birth of their children.

All three carrier couples were at risk for sickle cell disease and none of them underwent prenatal diagnostic testing. Rates of prenatal diagnostic testing and termination are lower for this condition than thalassaemia.[16] Our findings are therefore in keeping with this. One explanation for why these women did not proceed to prenatal diagnostic testing is that, despite undergoing carrier testing, they were unaware of the implications of such testing, i.e. they made an uninformed decision to undergo such testing. Offering carrier tests prior to pregnancy, *i.e.* pre-conceptually, could allow women and their partners to make decisions about prenatal testing without the time constraints that operate when testing takes place during a pregnancy.

## Strengths and weaknesses

This study is the first in almost 20 years to assess the psychological outcomes of SCT carrier detection, and the first to do so using standardised measures. However, due to the small sample, the findings should be generalised with caution. In addition, four of the carriers were known to the health-care system but not to the GP before the current pregnancy. It is unclear if these women were aware of their carrier status, and what the impact of this was on their emotional outcomes. While more carriers responded to the questionnaires than did non-carriers, nonetheless responses from over 30% of eligible carriers were not obtained. Given that non-responders to studies of this kind tend to be more anxious and depressed than responders,[98,99] the current study may have underestimated the emotional impact of antenatal carrier detection.

The results of the current study suggest that antenatal SCT carrier detection does not impact negatively on the emotional well-being of pregnant women. Longer-term follow-up on larger numbers of carrier couples is needed to estimate more precisely the extent and nature of the emotional impact on them and whether there are variations according to risk to a particular type of SCT disorder.

## Antenatal SCT screening in primary care – acceptability for women

These analyses examine the feasibility of implementing SCT screening in primary care in terms of its acceptability to women. There are many factors that determine the acceptability of antenatal SCT screening, including prior knowledge about SCT, the screening process and sociocultural background. This study uses women's perspectives to explore the acceptability of being offered antenatal SCT screening in primary care.

### Method and procedure

Interviews were conducted with a sample of women to ascertain their experiences of antenatal SCT screening. In total, 21 women and their babies' fathers, if consenting, were asked to complete an interview. For those who did not speak English, these interviews were conducted in the language of their choice, using an interpreter.

General practitioners asked eligible women in all randomisation groups if their contact details could be passed to the research team, so that the research team could contact them to inform them about the trial and seek consent to take part in the trial evaluation and interviews. For those willing to take part in the qualitative stage of the study, a researcher contacted women by telephone, in the first instance, to explain the study and seek consent to participate in an evaluation exercise, as well as a face-to-face interview. Interviews were then set up with consenting women.

A purposeful sample of women was obtained for this study in order to obtain data relating to a variety of backgrounds. A purposeful sample 'is one that provides a clear criterion or rationale for the selection of participants, or places to observe, or events that relates to the research questions'.[100] The demographic data of women is provided in *Table 30*.

Overall, 21 women were interviewed, with an average age of 29.5 years. Nearly half of the women were born in the UK and just over half were born outside the UK. Women were recruited across each randomisation group. In addition, we aimed to recruit women who varied in ethnic group, language and carrier status because one of the features of this study was to explore the impact of ethnic origin. The aim was not to 'essentialise' the data by looking at ethnicity in isolation from other variables. No fathers agreed to be interviewed, having been invited via mothers.

Of all interviews, 17 were conducted in English and four in a language other than English. The languages interpreted included Spanish, French and Somali. Although not perceived as good practice in qualitative research, in these cases an interpreter was employed. This was necessary because of the range of languages that we needed to be covered. During the process of interpretation we went for conceptual rather than linguistic equivalence. Women were given a choice as to where they preferred interviews to take place, either at their GP's practice, at Kings College London or in their home; 19 women preferred to be interviewed in their home and two at their GP's practice.

All interviews were carried out or supervised by an experienced qualitative primary-care researcher. Each interview lasted approximately 45–60 minutes. Women were given a £10 gift voucher in return for their time. The interviews were open ended and a semi-structured interview schedule was used to aid the researcher; this was developed during the pilot phase of the study and modified as data collection took place. The topic guide included:

- offer of antenatal screening (i.e. women's prior knowledge of SCT, the timing of the test, how the test was offered to her)
- decision about whether to accept or decline the offer of screening
- experience of receiving results
- reflection on the screening process.

Informal analysis began during the interview process. This enabled the researcher to clarify and probe emerging issues. The researcher began formal analysis of the interview data after the transcriptions process was completed. The data were analysed thematically across all groups, drawing on grounded theory using the method of constant comparison; common themes and ideas were identified and then categorised. It involved organising the data into defined categories and abstracting their meaning. NVIVO software package was used to organise the transcripts. A provisional, inductive coding frame was derived from the earlier stages of the analysis but was modified as new themes emerged. This was used to assign codes to the transcribed data. To increase reliability, some interviews were double coded by other researchers in the SHIFT team. The research team conducted all interviews and discussed transcripts to ensure

***TABLE 30*** *Demographic characteristics of the sample*

| | Number of women |
|---|---|
| ***Randomisation group*** | |
| Primary care parallel | 6 |
| Primary care sequential | 10 |
| Standard care | 5 |
| ***Self-reported ethnicity*** | |
| White | 8 |
| Black | 7 |
| Indian/Pakistani/Bangladeshi | 4 |
| Chinese | 1 |
| ***Carrier status*** | |
| Carrier | 7 |
| Not carrier | 10 |
| Not tested | 4 |
| ***Language of interview*** | |
| English | 17 |
| Other | 4 |
| ***Age (years)*** | |
| Mean 29.5 | |
| ***Place of birth*** | |
| UK | 10 |
| Outside UK | 11 |

strict quality control and shared understanding of the significant issues.

## Results

Analysis revealed a variety of perceptions and experiences relating to women's acceptability of being offering SCT screening in primary care at the time of pregnancy confirmation. These included:

- perceived benefits of early detection
- satisfaction with the level of control in decision-making when offered test by GP
- language barrier
- need for more information.

### *Perceived benefits of early detection*

Women were asked about their views on the most appropriate time to be offered screening. All women, irrespective of ethnic origin, believed that antenatal screening should be offered to women as early as possible. One woman spoke about the danger of late diagnosis:

> that it is very important to have it done especially in the early stage because it could be very dangerous leaving it and not want to find out, both of them could be dangerous. It's best to get over it, to know what's happening, if you have got the carrier so you can be treated or something like that because it could be very dangerous not knowing, leaving it too late.

Women talked about the difficulty of termination in advanced stages of pregnancy where the mother has started to 'bond' with her unborn baby. It was argued that there were more reproductive choices available if screening was offered at an earlier stage by the GP:

> Where if you're so far gone that … like 19 weeks obviously I could terminate if I wanted to but 19 weeks is a long time after going [to GP] at 6 weeks and then I'm already showing. So then I find out I'm a sickle cell sufferer and my child could suffer from the condition and it's not a nice condition … It's like if I did know from earlier on, you know, you can make that choice but so late in the pregnancy – it's not nice because even if you know that your child is suffering from something you have bonded with it already, you just want to continue with it. And obviously you want to continue with it but you aint going to know the full extent until she is born and then you're going to know exactly how she is suffering and then I don't know, are you going to get second thoughts after she's born? Thinking why should have I brought her into the world like this or should I, you know have kept her?

> Because it's your GP who is going to refer you to your midwife so it's better they do it so they know the risk you're going to have before they process anything more. It's better for my GP to get it done.

> I don't really see the midwife very often now. I've only had one appointment with her and I've not got another one until 26 weeks so it's quite late I think to wait for the midwife.

Most women expressed that they would undertake any screening if it meant that they could determine the health status of their unborn baby. All women expressed that they wanted a 'healthy' baby and emphasised the importance of obtaining this information as early as possible:

> Because I knew I wanted to carry a baby and I wanted a healthy baby so … if that is to protect myself and if I was in that early stage, and if I knew I would be carrying I would take any decision that will be safer.

Many women spoke of the importance of being prepared, either to continue with her pregnancy or for termination, and expressed that early diagnosis allowed for this:

> It's better to have it done earlier because you're just prepared for it. If you have a disorder you're prepared for it, yeah you might need a blood transfusion at your delivery … you are prepared for it, this is going to happen to you and this is how the child is developing and yeah you are quite prepared for it. it's better to have it done earlier yes.

> Well, actually, it allows you to … firstly you're best informed at the beginning but it also allows you to mentally get used to whatever issue there might be.

One woman spoke about her stressful experience of being diagnosed as a carrier of sickle cell at an advanced stage of her pregnancy:

> I think we should have screening the first time we see the doctor. Actually I think I was late for that test as well. When I went for that test they took my blood and in the end of my third or fourth month of pregnancy the results came, after that I know I was a carrier. They called my husband, and you know, it was like almost four months I had completed, so I was worried if my husband is also in that trait and maybe I have to go for abortion and in that condition after, you know, after four, five months it's very hard for anyone. So I think if they are offering that's a very good thing, but they should offer it a bit earlier and they should give the result early, as soon as possible because they take so much time in giving results, two or three weeks later, two weeks. That's a very bad part, I think, because till that time my husband's results came I was, you know, I was so worried what would be the result and what's going to happen. And that was almost the beginning of fifth month.

Two women believed that SCT screening should be done preconceptually:

> I think if you do the blood test before (pre-conceptually) and then you undergo pregnancy and you know that you're carrying a disease and then you won't go for any pregnancy but if you're already pregnant and then you undergo blood tests that will show that you may be carrying some disease then I think it's quite stressing and …

> I mean before thinking of planning a pregnancy I would convince them to have it done. It's better then.

***Satisfaction with the level of control in decision making when offered test by GP***

About half of the women felt that GPs offered screening in a way that facilitated informed choice. They reported being given time to consider if they wanted to accept the offer of screening:

> No, no it was all right because you get to make your own decision with no rush, it's not forcing you so you can easily make up your mind if you want or if you don't want, you're not under any pressure or any stress. You're free to say no or yes, it's your decision really.

> Actually he told me, you make up your mind about it, if you want to do it, you can come back here and make an appointment for it. If you don't want to do it it's okay. So he actually gave me time, but after like a week I went back in and made an appointment, and then they booked me in.

However, many spoke about GPs encouraging them to undertake screening. They said that GPs had positive views about the test and this influenced their sense of choice:

> The doctor did say that you've got to have a test done, it's for sickle cell and … my GP didn't give me a lot of details about it just that Asian women are more prone to have blood disorders, so just to save the risk of the baby you have this test done as well. So I didn't mind having the test done, she didn't go into detail … she sort of encouraged me as well that it's better to have it done … because Asian women were more prone to this disorder, that's the reason she gave me.

Some spoke about not being given a choice by their GPs but did not see that as a problem. This woman explained that she was highly satisfied with this approach:

> I don't think they gave a choice. They said go tomorrow for this test, like that. I'm totally happy, because it's actually beneficial for us, that's why they're saying it.

The majority spoke about their absolute trust in their GP: they believed their GP would recommend whatever was in their best interest. Women's expectations of the consultation process meant the GP could exercise considerable influence:

> I trusted her, you know, they want the best for you.

> Yeah, you had a choice, yes but why give a choice … if the doctor recommends it, you should do it.

> I was given a choice whether I wanted to have it done or not. She told me it was better to have it done. I did it because she told me to do it and I trust her.

> I don't know why, the doctor suggested it and I just followed their advice.

These views were more prevalent in South Asian communities where the doctor, according to our respondents, was greatly revered. Many, irrespective of ethnicity, believed that the GP has more authority than a midwife to offer screening. This is, therefore, not only about timing:

> A GP is more like, sort of more experienced you could say and … they know more about it so maybe yes it's better to have a GP you know say the idea of it.

There were four white women in the study who declined SCT screening on the basis of information received by their GP. Their GPs explained that their ethnic background did not put them in a high-risk category thus they did not see any reason for undergoing screening:

> Because I know that sickle cell anaemia and thalassaemia they're common in certain ethnic groups like the Afro-Caribbean and the Mediterranean that sort of culture. And so I thought 'why bother'?

### *Language barrier*

Several felt that language was a barrier to their understanding about SCT and the screening process. A lack of language support is a longstanding problem in the NHS.[101] Women often felt confused and ill informed about important decisions. One spoke about not being aware that she had undertaken screening:

> I didn't know I was taking a test for nothing. I just had a blood test done and they found out I was a carrier.

This woman spoke about her negative experience of being ill informed. She spoke about the frustration experienced when an interpreter had not been arranged for her:

> I would like to know more about it, if it is a serious matter, yes because I don't understand very well English then, I couldn't get the whole, you know … I didn't really know what was going on. It was a surprise because I never heard about it and I would have liked to know more about it. I understand you know but other words I can't understand and this is a very important thing, you know … I wasn't scared to ask for information, but the problem is I cannot understand. They can't explain to me everything, I asked them to send me an interpreter but they couldn't help me. It was my fault because I didn't ask them sooner to give me, to send me an interpreter.

Another woman was still confused at the time of interview. She had been sent a letter saying that she was not a carrier but she could not read English to understand the result:

> It affects me because I don't understand what it's all about. There was nothing in Spanish either … It was very difficult …The doctor just said 'we are going to do this blood test' and that's all so … I am confused till now because I don't know whether I have got it, the sickle cell condition or not.

### *Need for more information*

The majority believed information was an important aspect of antenatal care and felt the explanations they had received were inadequate:

> It's just nice when you go to your doctor for the first time to have a little bit of information of what's going to be happening to you and the things that you have to go through.

> No I want more information, the problem is I like to know more information you know the information wasn't enough.

Another woman emphasised the importance of information when making decisions:

> It's important because it's a guideline to help you make the right decision as to whether you really want to do it or not, yeah, I think it's really important.

Despite receiving an information leaflet, some felt that GPs should still spend more time explaining:

> when they explain it to you and then you read you get a more clearer understanding of it and then you can sit and make up your mind after you've finished reading. You can sit and make up your mind much easier rather than just reading the leaflet on your own.

A couple of women who had been diagnosed as carriers of sickle cell were still confused about the condition:

> I wouldn't mind knowing more. As a carrier I still don't know what it is.

Furthermore, some felt the explanations could have been made easier to understand. This was particularly applied to women who did not have English as a first language:

> A little bit more detail yeah. Maybe instead of relying so much on the form. Because I can read and write but a lot of people where I live, in my local area don't have a clue …

After being diagnosed as a carrier, this woman felt that she had been ill informed as she was not given enough information initially by her GP. This led to her being anxious and confused after receiving the result:

> I didn't really think I was a carrier, I didn't think I was a carrier, basically I didn't really think about it. When it came out I just found out that I was a carrier so … I really want to know more about it, whether it's going affect my baby or not, that's what I'm really concerned about …The doctor didn't give me that information.

This woman argued that GPs should be putting pressure on women to take this test:

> I was not expecting it but then I said okay it's rare and it can't be in me and like that. But when my results came and they were positive, at that time I was thinking they should actually influence everyone and give more information about this test because no one can say that this disorder is in them or not.

## Women offered care by midwives

Women offered screening in secondary care by their midwives were less aware of being offered SCT screening, which was offered with other screening tests:

> I can't recall a very serious or specific conversation about sickle cell. And maybe it was contained in a wider range of tests and I've not picked up on it, and it's just been not some of it's registered with me.

> She did was she went through like a list of stuff, they check for HIV, they check for this, this, this, this, hep. B whatever. And so you listen to this list and it probably was two of the things that are mentioned on that list. More information would have been better actually. Just I think just a bit more information at the time of that particular meeting with the midwife, I think that would be great.

Beyond this, there was little difference in the accounts of these women and those offer screening by the GP. Women offered screening by midwives believed that early screening was beneficial to be able to assess the well-being of the baby, as well as allowing time to consider options if a baby was found to be affected.

These women felt that their midwives encouraged them to have SCT screening, and took their advice believing they wanted the best for the baby:

> The midwife the first time she introduced herself, and she said, 'I'm going to do blood tests with you and some tests with you to check how the baby is' and because of the reason I went along with it to have all the blood tests.

They would, however, have liked more information, as this woman's narrative explains:

> I'd say it's [information] very important actually. Because I just think that you should be aware … you should be aware of all of the options that they are and the things that could potentially happen and things like that. And

I think that's, for me anyway, I like to know about things rather than not know about them.

## Discussion

The aim of this study was to describe women's acceptability of being offered SCT screening in primary care. Key themes identified were:

- perceived benefits of early screening
- satisfaction with level of control in decision-making when offered test by GP
- language barrier
- need for more information.

### *Perceived benefits of early screening*

The acceptability of SCT screening was high. All women, regardless of ethnic origin, recognised the benefits of early screening and believed that mothers should be aware of the health status of their unborn babies. It is possible that women's acceptance of early screening is due to an expectation of a healthy pregnancy – in other words, they do not think they will have to make a decision about whether or not to continue the pregnancy.

### *Satisfaction with level of control in decision-making when offered test by GP*

The women felt it was their maternal responsibility to follow advice of the HCP if they wanted to bring a 'healthy' child into the world. It could be deemed as irresponsible to reject screening against advice, particularly if there was subsequently a negative outcome. This is an example of women not wishing to be labelled as 'deviant'.[102] It demonstrates how individual preferences are made in relation to broader normative values and assumptions.

The study echoed previous work that has shown that women place total trust in their doctors.[103–106] The authoritative status of medical knowledge emerges as a recurrent theme, which has an impact on both informed choice and the acceptability of screening. The women's narratives indicate that they seldom questioned the doctors' decisions. This passivity can be explained by Porter and MacIntyre's (1984: 1197)[107] theory that women believe that available procedures must ultimately be the best option for them. The fact that a woman may feel vulnerable during her pregnancy could also explain the level of trust in the HCP.

### *Language barrier*

In our study it was found that women who did not speak English fluently found it difficult to communicate their needs. Women who did not have English as a first language were ill informed, and were often not being aware that they had undergone SCT screening. This led to frustration and dissatisfaction with health services.

### *Need for more information*

Many women expressed that they were given a choice, but also revealed that GPs presented the test in a positive light, encouraging them to undergo screening. This challenges the concept of 'informed choice'. It suggests that women's view of informed decision-making is not necessarily shared in formal policy. Beatie (1995)[108] points out that women's satisfaction with childbirth is influenced by their power in the decision-making processes, as well as their sense of control during the birthing process. Our study revealed significantly different results. In general, women were satisfied with their 'low' level of control in decision-making.

Many women revealed that they were less satisfied with receiving test results. Women talked about the lack of communication and were left ill informed about the meaning of results. It is interesting that women feel they have a greater need for information later in the process. This possibly relates to increasing awareness of their role as a 'good mother' and the responsibility for bringing a healthy child into the world.

## Strengths and weaknesses

Qualitative methods were used to explore the subjective experiences of women and to understand behaviour, meanings and interpretations that are attached to that behaviour. The MRC guidelines (2003)[109] assert that qualitative studies nested within much broader trials provide a better understanding of the views of participants and professionals' involved in the studies. These findings, although thematically valid, cannot be generalised in a the same way as a quantitative study. Although our sample is ethnically culturally diverse, the small sample size limits our conclusions about social class differences. Additionally, our study took place in London and does not reflect regional variations.

## Conclusion

Overall, women had positive attitudes towards being offered SCT screening in primary care at their pregnancy-confirmation visit. They did, however, identify a need for more information about the conditions (i.e. SCT) and the implications of testing.

# Chapter 8

# Feasibility of offering SCT screening in primary care

This chapter describes the qualitative analyses from interviews with HCPs. It aims to identify the major factors that influence the feasibility of offering antenatal SCT screening in primary care, for the purposes of facilitating a more responsive policy and practice to meets the needs of women.

## Background

There is little evidence about the best ways to successfully implement screening programmes in primary care. Policy and practice often assume an unproblematic approach to implementing new ways of working. Dissemination and implementation strategies, however, have costs that may outweigh the benefits of the new technology. Traditional models of implementation, which assume health-care providers and managers have the resources, skills and motivation to introduce new practices in their working environment, are often flawed because they neglect the barriers to introducing new practices.[110] Barriers to implementation exist at many levels, including the individual practitioner, the clinical team, the practice setting and wider organisational factors.[111,112] Implementation research has tended to focus on the role of individual health-care practitioners,[113] although even in a setting such as general practice, where clinical autonomy and discretion is relatively strong, there is evidence that practitioners can equally be a product of social and organisational circumstances in which they work.[114]

The evidence concerning the most effective way of implementing SCT screening among pregnant women is sparse, relying on speculation rather than empirical insight. Implementing screening in primary care is seen as especially difficult,[30,115] with the need to set up new practice systems serving as a major barrier to implementation. Other barriers include a lack of training and resources and enthusiasm among GPs to play a strong role.[22] Many GPs had little interest in screening, particularly given the many other pressures they had to deal with. It was also noted that very few GPs had much interest in SCT, compared with diabetes or general health promotion. Further, Qureshi *et al.* (2006)[116] found that GPs were more confident in providing prenatal genetic advice for CF carriers than thalassaemia carriers. These GPs also demonstrated poor awareness of the importance of rapid referral to diagnostic services. Several studies have investigated the negative attitudes of GPs and other health professionals towards prenatal testing in primary care, while also raising patient concerns about the quality of their care.[117,118] Further, patients from minority ethnic groups can be viewed by some professionals as a burden in primary care, creating another barrier to successful implementation.[119] Other barriers to good quality care include poor communication and a lack of collaboration between primary and secondary care.[115] In addition, HCPs also believed that there was little knowledge of screening among affected communities.[21,120]

In summary, there is limited evidence about the best ways to successfully implement screening programme in primary care. The current study builds on the available evidence by examining the feasibility of implementing screening in primary care. It explores the perspectives of GPs working in the general practices where screening was offered antenatally as part of the SHIFT Trial.

## Methods and procedure

Semi-structured face-to-face interviews were conducted with 34 participating GPs. The content of the interview varied according to roles, but covered the acceptability and feasibility of offering antenatal SCT screening in primary care. Informants were identified from amongst SHIFT-participating practices using a purposive sampling frame. A nominated person consented on behalf of the whole practice for two participants to complete tape-recorded interviews.

All interviews were carried out or supervised by an experienced qualitative, primary-care researcher in each of the clinics and recorded with informants' consent. Each interview lasted approximately 30 minutes. The interviews were open ended and a semi-structured interview schedule was used to aid

the researcher. This was developed during the pilot phase of the study and modified as data collection proceeded. The topic guide began with the general themes about the organisation of care of pregnant women within practices, followed by specific themes about the experience of offering SCT screening, and, finally, the obstacles and enabling factors to offering the test.

Data collection and analysis was an iterative process. Informal analysis began during the interview process to allow insights gained from one interview could inform subsequent interviews. As a result, the researcher was able to clarify and further probe issues that are being elicited giving further insight into the area under investigation. The researcher began formal analysis of the interview data *after* the transcriptions process was completed. The data were analysed thematically across all groups, drawing on grounded theory using the method of constant comparison; common themes and ideas were identified and then categorised. The data were organised into defined categories and their meaning abstracted. NVIVO (2006)[121] software package was used to organise the transcripts. A provisional, inductive coding frame was derived from the early stage of the analysis and modified as new themes emerged. This was used to assign codes to the transcribed data. To increase reliability, some interviews were double-coded by others in the research team. All interviews were conducted by VT.

# Results

## Barriers and facilitators of offering antenatal SCT screening in primary care

Analysis of the interviews revealed a range of perceived barriers and facilitators in relation to the feasibility of offering SCT screening in primary care at the time of pregnancy confirmation (*Table 31*). These have been categorised at three levels: organisational, professional and patient. These barriers and facilitators are linked, and, in some instances, are cumulative. For example, the difficulty posed by a woman not speaking English is exacerbated by time constraints in consultations. Similarly, women's positive attitudes towards care offered by GPs within a consultation would be less of a facilitator if patients did not hold positive attitudes towards SCT screening.

We now provide evidence for these facilitators and barriers by exploring the perceptions of the GPs.

# Organisational barriers

## Inflexible appointment systems

A lack of time during consultations was perceived as a major organisational barrier by the majority of GPs in each group practice. Many GPs felt the need to offer screening and, although not perceived as disruptive to the consultation, it was seen as an inconvenience. On average, GPs reported that an extra 5–10 minutes was required to offer SCT screening in a consultation. Some GPs stated that more time was spent offering SCT screening at the beginning of the trial, immediately after receiving training from the trial team. As the trial progressed, less time was spent on offering screening to patients.

> Time – I think the biggest thing was the effect of time. General feeling of just how awful it was to take so much time. (HCP017)

> Apart from making us late for consultations and therefore stroppy all afternoon and therefore later, and therefore probably not giving as good a service to other people as you could do, that's the main thing. (HCP025)

When asked about the feasibility of offering SCT screening in primary care, some GPs believed that perhaps it was best left to the midwives. They felt that patients are more likely to be offered informed choice if they were offered SCT screening by their midwife, who had more time to spend in each consultation, as one GP reflected:

> Yeah when they do all the booking bloods because that is when they have a bit more time to counsel them, they do all the triple screening for the Downs test, HIV and this would be another addition to that. I just wonder whether it might fit in a bit easier in that consultation. (HCP030)

## Women not understanding English

General practitioners mentioned women's inability to understand English as a major organisational barrier to offering the test. It meant that consultation time was extended, which, in turn, caused disruption to the GPs' schedules. This is a common problem for those working in primary care. Many do not have the organisational resources available to secondary care to offer interpretation services. GPs said that when patients did not have English as a first language

***TABLE 31*** *Health-care professionals' perceptions of the barriers and facilitators to offering SCT screening in primary care*

| | Barriers | Facilitators |
|---|---|---|
| Organisational | Inflexible appointment systems | Simple and flexible systems for offering SCT screening in primary care |
| | | Practice cohesion |
| | Women not understanding English | Training |
| Professional | Raising possible adverse outcomes in first antenatal visit | Positive attitudes towards SCT screening |
| | Negative attitudes of GPs towards offering SCT screening in primary care | |
| GPs perceptions of women's views | Women's negative attitudes towards undergoing SCT screening | Women's desire for healthy children |
| | Women's lack of awareness of SCT | Women's positive attitude towards care offered by GPs |

it often took a long time to provide a background explanation about the test. One GP stated:

> I mean, it's not difficult to discuss it but it's time consuming and that's, that's always the constraint. And we do have a significant number of patients who have difficulties with the English language and it's quite a subtle concept to get across to someone who doesn't speak English very clearly. So that … those were the main difficulties. (HCP023)

Another GP spoke of his frustration about attempting communication with particular communities who cannot speak English:

> I think so, yes. The new immigrants who are coming are a nightmare for all of us, particularly those who are coming from Eastern Europe and they speak Russian, Polish and some other mixture of things. Those are very difficult patients, they can … we usually communicate in sign language, it's very difficult. (HCP01)

Another GP used the strategy of delaying the offer of screening until the patient had a means of understanding clearly, as she explained:

> Sometimes it was difficult to get through to patients in the sense that there were language barriers and there were no translators and sometimes it just takes ages before you can get through to 'language line' [a translation service available by telephone] so I usually did ask them to come back. (HCP018)

# Professional barriers

## Raising possible adverse outcomes in first antenatal visit

Many GPs expressed concern about raising interventions with possible negative outcomes, such as SCT screening, in an initial consultation, when most women are feeling happy and excited about finding out about their pregnancies. This, perhaps, reflects a general lack of training, in which GPs find it difficult to break bad news. One GP felt that using the word 'termination' would cause women to be anxious about the test as well as cause her to be unnecessarily upset. She would therefore discuss SCT and the benefits of having the test but would avoid mentioning termination.

> I don't mention anything because it's like I make them disappointed, they can be upset or make them more worried. (HCP02)

Another GP argued:

> Well that was one of my arguments against having the screening really, is that I think that as soon as someone books in with a pregnancy to then discuss options for termination it seems highly inappropriate and I would say that really. (HCP032)

## Negative attitudes of GPs towards offering SCT screening in primary care

Another dominant theme emerging from the interviews was that some GPs held more general,

negative views about offering SC&T screening in primary care. One GP thought that difficulties in the implementation of screening would arise from the unreliability of doctors:

> Yes I think that in the main GPs are a bit unreliable. And I mean it's probably partly that they're doctors and not nurses and nurses are better at following instructions than doctors I think. (HCP031)

Some GPs mentioned that it was unacceptable and unnecessary to ask women to undergo multiple tests during pregnancy:

> One thing was ideally you would see a woman within a few weeks of her getting pregnant, do the test then and then she would see the midwife and get the rest of her blood tests done, in an ideal world. But often we were booking women late and then they were having a blood test for the sickle and then a week or two weeks later seeing the midwife having more blood tests and it seemed a bit unfair … (HCP010)

## Perceived patient barriers

### Women's negative attitudes towards undergoing SCT screening

General practitioners mentioned that they perceived women's attitudes as a barrier to offering the test. GPs identified several reasons why women might be reluctant to consider screening. Some women, particularly those from Northern Europe felt that the test was irrelevant to them and therefore not a priority, as described by one GP:

> . … a lot of people thought it was completely irrelevant to them and why were we talking about it and had much more pressing questions that they were interested in asking. (HCP013)

Some GPs saw women's moral and religious views as reducing interest and uptake of the test:

> My impression – and I haven't really tested this out – but my impression it's on religious grounds and they wouldn't consider a termination so there's no point, you know, they will accept what God has given them, is their attitude very often. (HCP023)

### Women's lack of awareness of SCT

A perceived lack of awareness among women about the role of screening was another concern of GPs. This lack of awareness arose not only because of language but also because of lack of awareness of SCT. Generally, people know little about the process or implications of genetic screening, and the problem might be greater among ethnic populations. GPs perceived that women were largely unaware of SCT before being offered this test. African and other black communities were perceived as more aware of sickle cell than were communities in which thalassaemia was prevalent. GPs generally believed that there needed to be greater awareness of thalassaemia in particular.

> Because I always just assume that patients of the Afro-Caribbean community know but not everyone is really aware and then again thalassaemia you would expect as well that certain people would know but maybe … some did but … (HCP018)

GPs felt that this lack of awareness meant that they needed to spend time on providing background information about these conditions before offering the test:

> I was actually quite surprised to see how many patients of Mediterranean or African Caribbean origin didn't really know [about SCT] and then people did have a lot of questions about the why and what if, so that takes a long time and trying to explain thalassaemia. (HCP018)

## Organisational facilitators

### Simple and flexible systems for offering screening in primary care

Many GPs felt positively about the simple and flexible systems set in place by the trial for offering SCT screening in primary care. Taking part in the SHIFT Trial meant that every GP was invited to a training session on antenatal screening for SCT and given an introduction pack to give to each pregnant woman. These packs included information for women, a father's pack, an NHS leaflet about SCT, a blood test request form and a notification of pregnancy form. GPs felt that these materials made it easier for them to offer SCT screening to women:

> Well I liked the presentation of the pack. I think it boosted your confidence when somebody said 'here's your pack' dollop and you just literally just pull out that one little folder, plastic folder per patient. That was nice because it made you feel 'yes it's going to be easy to do' … (HCP019)

> Obviously we had the initial training, and after the training obviously it was very helpful to have all the packs all there, ready, and us being aware. (HCP09)

> I think this sort of got structure, so you actually work from structure because you're aware, I used to have the red folder [SHIFT pack] there. Having it set out properly was very useful as well. If I had to pick up little bits here and there and not find the bits it would be much more difficult. (HCP015)

### Practice cohesion

General practitioners in small practices felt they had more control within the practice than GPs in larger practices where more organisational barriers may exist. Some GPs believed that there would be difficulties in implementing SCT screening if practices were not cohesive:

> Yeah. It's just in a small practice like ours it wasn't that difficult, a small practice like ours, you know, there's a small team, so communication is easier, but I don't know how this would work in a practice where there are ten GPs and 15 nurses and, you know, and lots of people coming and going … yeah. (HCP09)

Again, practice cohesion, an important factor, was referred to by two GPs:

> All practices are different to tell you the truth, but those practices who are … how can I say, not that organised … well more likely bigger practices will not be organised and small ones would be … (HCP01)

### Training GPs

Another emerging theme concerned the issue of training. It was agreed that GPs needed specialist training about antenatal SCT screening to be able to offer the test to women. Indeed, many GPs believed that the training provided by the SHIFT Trial had a positive effect on how they conducted their pregnancy confirmation:

> The training actually tried to crystallise the necessary information that I needed to pass on to the patient, and what I needed to obtain from the patient, so it, it made me more focused. (HCP03)

Despite GPs believing that training was important in teaching them to offer SCT screening in ways that facilitate informed choices, many believed that the test would be offered as routine due to time constraints:

> I think the doctors need to be well trained to talk about the test and I think there would be a tendency as time went on to just go this is what you have done because this is what we do, rather than the full explanation which was involved in the trial because you can't afford that amount of time to explain things thoroughly all the time. (HCP010)

## Professional facilitators

### Positive attitudes towards SCT screening

Many GPs emphasised the importance of educating their patients about SCT, perceiving there to be a lack of awareness about them. Having seen first hand the effects of these conditions not only on children but also their families, GPs were acutely aware of the importance of this information:

> I mean first of all the practice is mainly dominated by a south Indian population, or south Asian you can say generally and thalassaemia is, it is common and we have got a few patients with thalassaemia major and we can see what they're going through. (HCP01 – Group 1)

Earlier diagnosis was viewed positively. It meant that women had more time to consider their options and if they choose termination, would experience less physical trauma the earlier the procedure. One GP explained:

> Picking things up earlier which means you know what's going on. You are going to want to know this sort of thing earlier rather than later and if you find this out early then it's still a horrible thing to be thinking about but at least you are getting people into service quickly and the whole process, if they were to go for a termination, is obviously more physically

> traumatic the later you leave it as well. (HCP012 – Group 2)

Another GP talked about experiences with women who regretted not having known prenatally about their children's health status:

> Because we've seen the consequences of when mothers have found out that their children have sickle cell, have a haemoglobinopathy and it's been quite distressing for them and they wished that they knew beforehand. (HCP020 – Group 2)

## Perceived patient facilitators

### Women's desire for a healthy child

Women's desire to have a healthy child was perceived as a facilitator for the successful implementation of SCT screening in primary care. All GPs felt most women held positive views towards SCT screening. When asked why they believed that women were so compliant, GPs sensed the sole motivation for women's positive perceptions of SCT screening was the mother's moral stance, that is, her obligation as a mother to undertake any test that would benefit her unborn baby:

> Because of the explanation about the health of their baby, of knowing a little bit more about the health of the baby and it's something that they can pick up and I think that's a priority I think when you come. (HCP017)

Ultimately, mothers want what is best for their babies, and at the same time, they want to fulfil their role as a 'good' mother, as one GP proposed:

> Because it's to do with pregnancy and children and not just their lives I guess. (HCP025)

### Women's positive attitudes towards care offered by GPs

Despite doubts about the ability of primary care to implement SCT screening, all GPs, except one, said they presented the test in a positive manner, encouraging women to have the test. Reasons given for this approach was that they believed that women would want whatever was available. Some GPs recommended that pregnant women underwent the test for safety reasons. In addition, GPs believed that women would happily accept their advice if it meant that their child would benefit. Many GPs felt women expected them to take this approach:

> We didn't talk much about choice, I mean maybe it only comes under the assumption that they have come for it and I'm offering what is available. (HCP01)

The majority of GPs automatically believed that their own positive views of the test should automatically be viewed this way by patients.

> I think fortunately your patients trust you so if you say this is what we think is a good idea, because it is you know, certainly there's no harm will come of this, it can provide useful information so … you know there's no … it's not like you're offering something to them which they have any particular reason to be fearful of, it's just one additional blood test. (HCP012)

Again, one GP talked about doctors being held in high esteem in many cultures. Some GPs were not offering choice as they depended on their patients to follow recommendations based on these cultural beliefs about the doctor, as this GP expressed:

> Generally they usually go on what we say anyway because … Because I think a lot of those cultures, the doctor still knows best even though we try and portray things differently … it's a joint decision … but you know that's one of the things … (HCP020)

Another GP agreed with this notion of the revered doctor:

> I think what happens here the patients are relying on the doctor more, you know whatever they feel that the doctor says is better for them. Even like small, small things they don't understand, the community is such you know? (HCP021)

## Discussion

Overall, GPs included in the study were enthusiastic about offering antenatal SCT screening. They believed that screening would improve the health care they offered their patients. In particular, they perceived that screening early in pregnancy would provide important additional options for pregnant women. They did, however, perceive a number of barriers as well as facilitators.

The main organisational barrier described was inflexible appointment systems. GPs believed that there was insufficient time to offer screening in primary care. Time, or the lack of it, is a common theme in GPs' accounts of their working activities.[122] The majority of GPs felt that while they had provided women with a choice, the lack of time was a major barrier to facilitating informed choice. Another major barrier to implementation, and one closely related to a lack of time in the context of patient–practitioner consultation was language. Patients who did not have English as a first language were perceived as challenging, often burdensome,[123] and less likely to be offered screening in a way that would facilitate informed choices. Poor communication between doctor and patient has been attributed to language differences, and associated with dissatisfaction with health services. A study of immigrant women in Australia found that their lack of English and the providers' inability to use, or interest in using, *their* language generates feelings of frustration.[124] In the current study, the absence of a shared language was more problematic, particularly as GPs suggested that the use of interpreters was not feasible due to a lack of this resource in primary care. This finding highlights the need to develop systems, including evaluation, that facilitate the use of interpreters in primary care to ensure equity of access for people who do not speak English. This, however, is a longstanding problem.[101]

Practitioners face a number of factors militating against women making informed choices in relation to antenatal screening. These include the offer of a test being perceived as a recommendation to have it, and a lack of time to present choices fully.[125] Although most informants in our study expressed the view that patients were given a choice as to whether to undergo screening, informed choice was perceived as difficult to implement for many reasons, including time constraints, language barriers and patient reliance on GP recommendation. However, the quality of decisions made by women in the three trial groups did not vary, suggesting that the decision quality was not lower if the test was offered by GPs.

The current study supports the findings of other studies that suggest the implementation of antenatal screening for haemoglobinopathies in general practice may be difficult.[26,30,115] A low priority, for example, may be placed on activities that are not part of new performance and quality targets in the UK GP contract. More broadly, introducing antenatal screening in primary care involves more than the offer of a test. It occurs within a historical and social context, in which roles and responsibilities are constantly being negotiated and re-negotiated among the key stakeholders, such as patients, midwives, GPs, strategic health authorities, hospitals and the Department of Health, as they support, implement and challenge normative values and assumptions about health-care provision, of which screening for genetic conditions is part.[126] The implementation process has been shown to be shaped by the ability of stakeholders to impose their different interests and agenda.[127] In the context of this study, GPs beliefs and attitudes and their working practices acted as both facilitators and barriers to implementation.

General practitioners perceived the need for good communication at all levels. In addition, GPs in our study expressed the view that implementation of SCT screening in primary care may be facilitated when factors such as practice cohesion and GP training are addressed. For example, GPs suggested that smaller practices, where GPs exercised more control, would be better equipped to accommodate SCT screening than would larger practices where good communication systems are not in place. Often GPs from larger practices, who regularly employed locums, felt that SCT screening in primary care was not feasible.

Women's generally positive attitudes towards the general care offered by their GP was perceived by GPs as facilitating the introduction of SCT screening in primary care. Trust (or lack of it) is fundamental in understanding this.[123] GPs linked trust with the woman's moral responsibility to her child. That is, GPs perceived that women underwent screening because they wanted a healthy baby, feeling obliged to comply with medical advice, advice which most women trusted implicitly. Women who do not comply with the authorial knowledge regarding the value of technology in childbearing are ultimately held responsible for the health of their baby.[105] This has implications for informed choice. That is, women's trust in doctors can undermine the concept of autonomy embedded in informed choice. An alternative viewpoint is that women who act in line with the values of significant others, such as GPs, can exercise an informed choice if the individual 'chooses' to act in line with the attitudes of significant others.[128]

General practitioners had positive attitudes towards antenatal SCT screening, as they believed in the benefits of early diagnosis in facilitating timely

choice for pregnant women, having seen the effect that sickle cell disease had on their patients. They expressed the importance of educating patients about these conditions, particularly those at risk.

## Strengths and weaknesses

Qualitative methods were used in this study to provide a deeper understanding of GPs' subjective experiences. This extends work by Thomas and colleagues (2005)[26] by providing an in-depth analysis of GP's perceptions about implementing antenatal SCT in primary care. The findings documented in this study are based on self-reports of GPs based in high-prevalence areas, who were taking part in a trial. Such GPs may more be open to the idea of antenatal SCT screening than other GPs, and may not be representative of GPs as a whole. Observational data of the encounters between GPs and women and their partners may provide a different account. Our results present perceptions and experiences, and some of these may be based on generalisations or, perhaps, even myths. The aim of this paper is not to interrogate these in any great detail or determine whether they are 'true' or not. However, what this paper does attempt to do is to explore how their meaning is expressed in the context of service delivery.

## Conclusion

Overall, GPs were positive about offering antenatal SCT screening. They identified a number of barriers and facilitators, at organisational, professional and patient levels, which could usefully be considered in the implementation of such screening within primary care.

# Chapter 9
# Conclusion

## Main findings

In areas with high prevalence, offering antenatal SCT screening as part of the pregnancy-confirmation visit in primary care significantly increases the proportion of women screened before 10 weeks (70 days), from 2% in standard care to between 16% and 27% in primary care. It is important to note that the majority of women remain unscreened at this gestational age.

There are two likely causes for this:

- *First, nearly 50% of women were not offered screening before 70 days* This could be due to late confirmation of pregnancy or GPs failing to offer screening at the pregnancy confirmation visit. GPs attributed their failure to offer screening to women who attended primary care by 10 weeks to lack of time, language barriers and lack of training.
- *Second, there were substantial delays between the offer of screening and the screening test* These delays may be due to women taking time to make their decision about whether to be screened, or they may represent systemic organisational problems that led to delays in the availability of blood tests, for example the phlebotomy services in primary care did not always allow same-day testing.

Fewer than 5% of fathers underwent carrier testing. Of the fathers offered parallel testing in primary care, less than 3% were tested by 77 days' gestation. While this was significantly higher than the numbers of father tested using sequential father testing, the overall number is very low. This raises questions about the use of parallel testing in this context.

Overall, 17 women knew their couple carrier status by 77 days. Again, this number was significantly higher for those offered parallel father testing in primary care, but the numbers are still low. The reasons for this are unclear, but, for carrier women, the failure to screen fathers means that a couple's carrier status cannot be determined.

Offering screening in primary care requires additional resources. The transfer of screening into a primary-care setting is associated with an increase in costs to the NHS of between £31,000 and £52,000 per 10,000 pregnancies, depending on the screening approach considered. The cost-effectiveness analysis results indicate that the NHS would have to pay, on average, £12 to screen one additional pregnant woman before the 10-week threshold (using the primary-care sequential screening process). An important caveat relating to the cost-effectiveness results concerns the paucity of data on the additional costs associated with the screening process. As part of the trial, data were collected on consultation times but these data were partial and not straightforward to analyse and interpret. Therefore, it should be recognised that if primary-care screening could be undertaken without extending the consultation by the 3 minutes estimated in our analyses then, unsurprisingly, the cost-effectiveness results for such screening would look considerably more attractive.

Whether this is an efficient use of resources will depend upon the values attached to early screening and the consequences that arise from its implementation. It is unclear how much women value early screening for SCT carrier status. The proportion of women screened by 26 weeks was similar across the trial arms: an early offer of screening did not result in more women undergoing testing. This suggests that women may not perceive early screening to be more valuable that later screening. Studies of early screening for Down syndrome have demonstrated that women value the safety and detection rates of screening more highly than screening early in pregnancy, in contrast with HCPs who value earlier tests more highly.[129] Note that these findings may not be applicable in this context as detection rate does not vary by gestation. They do, however, highlight the importance of ascertaining the values of users and not assuming that these will be shared by those providing the services. Alternatively, similar uptake rates when the test is offered later in pregnancy make reflect women's lack of understanding of the

potential benefits of earlier testing. For example, they may not be aware of the possibility of PND or termination of pregnancy.

The principal value of early testing is that it provides carrier couples with the option of prenatal diagnostic testing in the early stages of pregnancy and, for those found to have an affected pregnancy, the option of a termination at an early stage of pregnancy. The evidence regarding the strength of value attached to earlier terminations is weak. There is evidence to show that the proportion of women undergoing PND following the diagnosis of sickle cell disorder or thalassaemia is lower the later in pregnancy the PND is made.[15,16] However, these are observational data that may be subject to ascertainment bias (those more ambivalent about PND or TOP may present later in pregnancy for testing). The data from the current population-based trial suggested relatively low interest in prenatal testing, regardless of gestational age. Of the 14 carrier couples detected, none went on to have PND. Two women opted for PND based on maternal carrier status only. These are very small numbers but they raise an important question that deserves systematic study: how much do couples value PND for SCT, and to what extent does this vary with the gestational age at which tests are offered, carrier status is discovered, and the condition identified?

Although the data on sickle cell disorder and thalassaemia were aggregated in this trial, there may be important differences, between and within the two conditions, which influence the behaviour of at-risk couples, for example the clinical effects, treatment options and prognoses. In addition, the demographic and ethnic characteristics of the at-risk populations for the two conditions are different: sickle cell disease primarily affects African Caribbean couples, while thalassaemia primarily affects Mediterranean, Middle Eastern and Asian couples. These differences need to be better understood.

## Implications for current services

The conduct of the trial and its results suggest areas demanding immediate attention for improvement.

1. The delay between the offer of a screening and the test being carried out is unacceptable. The reasons need to be analysed in order to reduce unnecessary delays and allow women time to make decisions.
2. Communication of test results seems ineffective for many women. Although not quantified as part of the trial, we became aware of many women who had undergone carrier testing previously, but primary care had no record of this. For example, four carrier women were offered testing in primary care but the trial team found a record of previous test results either in the laboratory or at a sickle cell centre. The proposed NHS integrated electronic health record has the potential to solve this problem.
3. Many women had low levels of knowledge and understanding of the conditions and the screening process. Additional resources will be required to improve levels of knowledge and understanding, particularly in those with low levels of education.[130] Whether these additional resources are justified depends on the value attached to informed choice in this context.
4. Generalisability to other high-prevalence areas. The trial was conducted in areas with high prevalence of SCT with a diverse minority ethnic population. While this may raise some questions about the generalisability of the findings to less ethnically diverse areas, the findings are likely to be applicable in inner-city areas across the world where SCT are prevalent. The generalisability to low-prevalence areas requires further work to investigate the feasibility of offering a screening test in primary care, where the conditions may not be perceived as clinically important.

## Designing services to achieve knowledge of SCT carrier status early in pregnancy

The results of this trial show that offering antenatal SCT screening for SCT in primary care as part of the pregnancy confirming visit is feasible, acceptable to women, and effective in increasing the proportion of women screened before 10 weeks.

In the intervention arms of this trial, many women were not screened early in pregnancy and very few couples determined their carrier status. This raises the question of whether this is the most effective model for screening.

Higher rates of early screening might be achieved by using a multifaceted approach, including some, or all, of the following:

- The incorporation of early SCT screening into routine primary care and midwifery practice, including the setting of targets and the provision of financial incentives for GPs and/or midwives to see and screen women early in pregnancy. Note that there may be ethical objections to financial incentives relating to screening.
- There is a need for more clarity about the organisation and delivery of antenatal care to reduce further the delay in offer and uptake of screening and to improve communication about the test and its result. It has been suggested that the majority of women could receive midwifery-led care from the outset (Redshaw and Rowe 2006). There could also be an opportunity to expand the role of pharmacists, as many women obtain pregnancy test kits from pharmacies.
- Preconceptual screening in conjunction with other health interventions, such as at the time of teenage rubella and human papillomavirus (HPV) immunisation, or as part of a local initiative in high-prevalence areas.

It should be noted however that the NHS SC&T Screening Programme will identify carriers of sickle cell trait in the neonatal period, meaning that in the future many will know carrier status before pregnancy. Individuals born abroad will not have been screened through this programme and will thus still require antenatal screening.

At the time of writing, 'polyclinics' are being introduced in London in line with proposals laid out in Lord Darzi's report 'Healthcare for London: A Framework for Action'. It is unclear what impact this will have on services or if 'polyclinics' will be introduced throughout the country.[131] The research findings must be considered in the context of changes to the delivery of primary care: the introduction of 'polyclinics' may affect the uptake of antenatal screening in primary care.

## National Screening Committee criteria

The National Screening Committee (NSC) in England uses a set of criteria by which to judge whether a screening test should become a programme. Antenatal SCT screening was deemed to meet these criteria as part of the decision to develop and implement a national programme. The SHIFT Trial informs three of the 22 principles (see Appendix 5, NSC criteria) guiding the implementation of any screening programme, which concern the acceptability of the programme, the balance between the benefits and harms from screening, and the opportunity costs of screening:

- 1. *Principle 14* There should be evidence that the complete screening programme (test, diagnostic procedures and treatment) is clinically, socially and ethically acceptable to health professionals and the public.
  - GPs were enthusiastic about offering antenatal SCT screening. They believed that screening would improve the health care they offered to their patients. In particular, they perceived that screening early in pregnancy would provide important additional options for pregnant women. Women also had positive attitudes towards being offered SCT screening in primary care at the pregnancy-confirmation visit.
- 2. *Principle 15* The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).
  - The results of the current study suggest that antenatal SCT carrier detection does not appear to impact negatively on the emotional well-being of pregnant women. Follow-up of larger numbers and over a longer time frame is required.
- 3. *Principle 16* The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money).
  - The key policy and value-for-money question is whether, for areas of high prevalence, where universal testing is currently being applied, the NHS should be willing to pay, on average, £12 to screen one additional pregnant woman before the 10-week threshold. This research suggests that important gains in early screening rates can be achieved, using the primary-care sequential screening process, at a rather modest cost. Whilst the early screen potentially gives key information to facilitate informed decisions on subsequent

investigations and actions in relation to the pregnancy, the true value associated with providing women and couples with such early information, however, is unclear at this stage.

## Recommendations for research

The following recommendations are equally weighted.

1. The principal value of early testing is that it provides carrier couples with the option of prenatal diagnostic testing in the early stages of pregnancy, and, for those found to have an affected pregnancy, the option of a termination at an early stage of pregnancy. The evidence regarding the strength of value attached to earlier terminations is weak. It would be useful to determine the impact of gestational age at screening on uptake of prenatal diagnostic testing, and reproductive decisions following the detection of affected pregnancies.
2. The values attached by individuals and society to having information about SCT carrier status early in pregnancy. From this trial, it is hard to ascertain the reasons why women did not have screening. It would be useful to explore their reasons, and to determine if their decision was an informed choice.
3. Low uptake of fathers could threaten feasibility of early screening. Without father testing, there is no early knowledge of couple carrier status, and reproductive choices are not facilitated. Limited test uptake may be explained by high levels of social and material deprivation in the trial area or if biological fathers are not registered at the same practice as the mothers. Research needs to identify the factors limiting the uptake of testing by fathers in order to determine how they can be addressed.
4. Exploring other models of care to increasing the proportion of women screened by 10 weeks' gestation. Possible mechanisms include exploring further the role of midwifery, the use of Quality Outcomes framework in primary care or increasing the role of community pharmacists.
5. The results of the current study suggest that antenatal SCT carrier detection may not impact negatively on the emotional well-being of pregnant women. Longer-term follow-up on larger numbers of carrier couples is needed to estimate more precisely the extent and nature of the emotional impact on them and whether there are variations according to risk to a particular type of SCT disorder. Due to the small sample, the findings in this trial should be generalised with caution.
6. An important caveat relating to the cost-effectiveness results concerns the paucity of data on the additional costs associated with the screening process. The cost-effectiveness results are highly sensitive to the value of this parameter and further data collection to assess the true impact on consultation length of adding screening in primary care would be helpful.

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## Ethics committee

Ethics committe approval was granted for all of the studies reported in this monograph.

## Contribution of authors

The trial was designed by Theresa Marteau, Elizabeth Dormandy, Tony Ades and Martin Gulliford with additional contributions from all other authors.

The analyses for Chapters 2, 4, 6 and 7 were all led by Martin Gulliford. The analyses for Chapter 5 were led by Stirling Bryan and Tony Ades. The qualitative analyses for Chapters 7 and 8 were led by Michael Calnan and Karl Atkin. The drafting of the report was led by Elizabeth Dormandy and Theresa Marteau with contributions from all other authors.

All authors read the final report and gave their approval.

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# Appendix 1

# Maximising recruitment and retention of general practices in clinical trials: a case study

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## Abstract

- *Aim* To formulate hypotheses about effective ways of recruiting and retaining practices to clinical trials based on a case study.
- *Design* Case study of practice recruitment and retention to a trial of delivering antenatal sickle cell and thalassaemia screening.
- *Setting* Two UK Primary Care Trusts with 123 practices, with a high incidence of SCT and high levels of social deprivation.
- *Outcome measures* Number of practices recruited to and completing a trial.
- *Methods* Practices were invited to take part in the trial using a Research Information Sheet for Practices. Invitations were sent to all practice managers, GPs, practice nurses and nurse practitioners. Expenses of approximately £3000 per practice were available. Practices and the research team signed Research Activity Agreements, detailing a payment schedule based on deliverables. Semistructured interviews were completed with 20 GPs who participated in the trial.
- *Results* Four practices did not agree to randomisation and were excluded. Of 119 eligible practices, 29 expressed an interest in participation. Two practices withdrew from the trial; 27 practices participated; two hosted pilot studies and 25 completed the trial, giving a retention rate of 93% (27/29). The 27 participating practices did not differ from non-participating practices in list size, number of GPs, social deprivation or minority ethnic group composition of the practice population.
- *Conclusion* Three factors appeared important in recruiting practices: research topic, invitation method and interest in research. Three factors appeared important in retaining practices: good communication, easy data collection methods and payment upon meeting pre-agreed targets. The effectiveness of these factors at facilitating recruitment and retention requires assessment in experimental studies.

*Keywords*: primary health care; clinical trials; recruitment; retention

## How this fits in

The focus of research into chronic conditions will shift from hospital to primary care as these conditions are increasingly managed in primary care. There is limited evidence, however, regarding the factors that facilitate recruitment and retention of general practices in clinical trials. A case study describing recruitment and retention of 25

practices into one clinical trial is used to generate hypotheses about effective methods.

## Introduction

Research activity in primary care will increase as the number of chronic conditions managed in primary care continues to rise. For example, the recent 'Roadmap' published by the Royal College of General Practitioners asserts 'virtually all health problems could be dealt with in primary care'.[1] It is therefore pertinent to consider the factors that facilitate research in primary care.

Recruiting and retaining general practitioners to participate in trials is challenging.[2–4] A recent review identified the lack of evidence about factors associated with recruitment to research of HCPs in primary care.[5] A range of interventions, including the use of printed educational materials, financial incentives, reminders, computer prompts and trial organisation, were described, but it was noted that there was an absence of evidence regarding their effectiveness. Experience from seven dyspepsia trials indicated that organisational strategies, such as the use of experienced researchers, methods of identifying eligible patients, GP workload and simplicity of patient eligibility criteria, may be more effective than more specific strategies at increasing recruitment in primary care.[5] In addition, concerns have been raised that the most successful recruitment strategies may lead to biased results. For example, the 'physicians recruiting physicians' strategy leads to acceptable recruitment rates but may not include representative practices.[6]

One example of a potentially effective approach to practice recruitment that is built on an intimate knowledge of research in primary care involves the use of Research Information Sheets for Practices.[7] These provide a template for the generation of clear and succinct information about a trial or research study. Recipients report these provide a good basis for practices to decide whether to participate in a study.[7] There has, however, been no formal evaluation of their effectiveness in recruiting general practitioners and practices to research.

While there are several published case studies describing the recruitment of practices to trials, there is limited evidence on the strategies most likely to achieve retention of representative primary care practices to trials.[8] In a US study, 22% (46 out of 210) of practices dropped out of a trial of cancer prevention in primary care within 5 months of agreeing to take part in the trial.[9] There is a lack of evidence of factors associated with successful retention of practices in primary care trials. Failure to retain practices may also reflect a failure to recruit participants, and there is some evidence on failure to recruit participants in primary care.[10–12] Prout and colleagues[13] interviewed nine GPs and one practice nurse after they had recruited varying numbers of children to a trial. Good trial organisation, simple documentation and trial procedures were reported as facilitating recruitment. While this evidence points to features associated with successful recruitment of participants by GPs there is limited evidence or guidance on strategies to successfully retain practices in trials.

Research networks of practices have been set up in the UK and elsewhere to facilitate the recruitment of practices to clinical trials and other research studies and to encourage primary care workers to undertake their research. The first primary care research network in the UK was the MRC General Practice Research Framework (MRC-GPRF), set up in 1973 for an MRC-funded trial of treatment for mild hypertension. In 1986 this was developed into a national research resource. The Framework now provides research access to 10% of general practices in the UK, although these practices are not representative of UK general practices as a whole.[14] The Primary Care Research Network (PCRN)was set up in March 2007 to increase the number of patients recruited or involved in research in primary care.[15] Neither network, however, currently provides published guidance on recruitment and retention of primary care practices.

The aim of the current paper is to present a detailed case study of the methods used to recruit and retain general practices in a clinical trial conducted in primary care, to form the basis for formulating hypotheses about effective ways of recruiting and retaining general practices to clinical trials.

## Methods

### Study design

This is a descriptive case study of the recruitment and retention of general practices into a cluster randomised trial, SHIFT (Screening for Haemoglobinopathies in the First Trimester).[16] The trial aimed to assess the effectiveness, feasibility and acceptability of delivering antenatal Sickle

Cell and Thalassaemia (SCT) screening in primary care. The run-in data from this trial are reported elsewhere.[17]

## Setting

The study took place in two UK inner city primary care trusts (PCTs) with 123 general practices. The PCT areas are ranked among the most deprived in England (sixth and 13th out of 354 boroughs) and about 40% of their total populations are from minority ethnic groups.[18] Six per cent of pregnant women in both areas carried a clinically significant haemoglobin variant.[19] A universal screening policy was in place in the PCTs at the time of the trial, i.e. antenatal SCT screening, was offered to all pregnant women regardless of ethnicity.[20]

### *Measures*

Number of practices participating in and completing the trial. The target was 24 practices, as power calculations indicated that data from 24 practices would provide sufficient power to answer the trial research question.[16]

### *Sample*

All general practices in two PCTs ($n = 123$). These practices included 123 practice managers, 450 GPs, 150 practice nurses and nurse practitioners at the practices. At least one GP from each intervention practice was interviewed at the end of the trial to assess GPs experiences of participating in the trial ($n = 20$).

## What practices were required to do

Practices provided anonymised data on gestational age at first visit, gestational age at testing, and demographic data (age, parity and ethnicity) during the run-in phase of the trial. These data were collected by GPs, practice nurses and practice managers. The run-in phase lasted for a minimum of 6 months or until data on 33 eligible pregnancies were obtained. This was followed by a minimum 7-month intervention phase, when practices offered antenatal SCT screening to women, according to the randomisation group. The randomisation groups were:

- *Group 1* In primary care, when women first report their pregnancies, with partners offered testing at the same time.
- *Group 2* In primary care, when women first report their pregnancies, with partners offered testing later and only if women are identified as carriers.
- *Group 3* In community-based secondary care, when women are booked by midwives with partners offered testing later and only if women are identified as carriers.

This was a cluster randomised trial with practice as the unit of randomisation. During the intervention phase, practices collected anonymised data as described in the run-in phase. In addition, eligible participants were asked by their GPs if the research team could contact them to invite them to take part in the trial evaluation. Women who agreed to be contacted by the research team were contacted in their preferred language, using a telephone interpreter if necessary, and consent was sought to take part in the trial evaluation. Finally, intervention practices were asked to nominate two HCPs for an interview exploring the feasibility of offering antenatal SCT screening in primary care. Run-in data collection started in the first practice in June 2005 and the intervention data collection was completed in the last practice in July 2007.

### *Procedure*

Using methods described in the literature and those based on the experiences of the research team, we developed and implemented the following strategies to recruit and retain practices in the trial.

**Invitation**

1. *Preparation of invitation and Research Information Sheet for Practices* Extensive drafting of the invitation letter and RISP was undertaken with input from three GPs on the research team and two GPs from the participating PCTs. The information sheet was tailored to each PCT and contained information about the low proportion of women offered antenatal SCT in the first trimester in each PCT.
2. *Sending invitations* Letters of invitation, together with an information sheet (see Appendix 1), were sent to all practice managers, GPs, practice nurses and nurse practitioners in the two PCTS ($n = 723$ letters). The invitation letters included an endorsement of the trial from the local PCT. They were tailored to each job title and signed by the trial manager, principal investigator and a local practising GP.
3. *Follow up of invitation* The trial manager contacted every practice manager within 2 weeks of practices receiving invitation letters to assess practice interest in trial participation. All

practices that expressed an interest in the trial were visited to discuss the trial in more detail.

**Costs**
About £3000 was available for each practice that completed the trial: the exact amount paid varied between £2100 and £3900, dependent on randomisation group and practice size. This covered the administrative costs of providing anonymised data, costs of offering antenatal SCT to pregnant women and locum costs for attending training and interviews. A payment schedule was detailed in a Research Activity Agreement, which practices were asked to sign if they wished to participate in the trial. Monies were paid in three equal portions at three time points: completion of the run in data collection, completion of the intervention phase and completion of GP interviews.

**Communication**
Open communication between practice and the research team was encouraged in order to facilitate early problem-solving. A link person in each practice was identified as the main practice contact for the trial. Weekly contact was maintained between this nominated person or a deputy and a nominated person in the research team for each practice during the data collection periods. This was the usual route of communication between the practice and research team. All GPs, practice nurses and nurse practitioners in each practice were invited to attend a 3-hour in-house training session for practices randomised to Groups 1 or 2, and a 1-hour in-house training session for practices randomised to Group 3. It should be noted, however, that the initial practice information sheet described the need to attend a 2-hour training session. The above strategy was designed to ensure that any problems the practice had in adhering to the research protocol (identified by the practice or the research team) could be identified and solved early.

During the 2-year trial period, three newsletters were produced to describe trial progress. These were circulated to all participating practice managers, general practitioners, nurse practitioners and practice nurses. Practices were invited to contact the research team for additional training for new members of staff. Two practices requested this. Data monitoring by the research team identified five practices that had not informed the research team of all eligible pregnancies. The trial manager visited these practices to retrain them in the research protocol. Retraining focussed on reminding practices about the trial and the need to inform the research team of all eligible pregnancies.

**Pilot sites**
Two practices acted as pilot sites for the trial. The aim of the pilot was to (1) identify robust methods of data collection and (2) assess the feasibility of trial methodology in the everyday primary care setting.

**Data collection**
Two methods of data collection were used in this trial. First, specially designed computer templates linked to routine antenatal care templates were installed on all participating practices' computer systems to facilitate anonymised data collection without the need to click on a second icon or open a separate programme to record trial data. Second, packs to facilitate data collection and recruitment were distributed to each clinician at the training sessions. These included a pack for every pregnant woman containing: (1) an information leaflet about sickle cell and thalassaemia in English; (2) an information leaflet about the trial in 12 languages; (3) a manual data collection form for every confirmed pregnancy to be faxed to the research team; and (4) a summary of the research protocol. These methods were developed following work in the two pilot sites that identified the need for robust, flexible and simple data collection systems.

Approximately 6 months after training (which marked the end of the intervention phase of the SHIFT Trial), informal face-to-face interviews were conducted with 20 GPs from practices randomised to Group 1 and 2. Part of the interviews explored GPs' views on why their practice participated in the trial. Interviews lasted approximately 30 minutes and were held in a private room at the practice. All participants agreed to be audio-recorded.

## Results

Of the 123 practices in the two PCTs, four practices were ineligible because they did not agree to be randomised. Two practices indicated they did not agree to randomisation *before* expressing an interest in trial participation, and two practices indicated they did not agree to randomisation *after* expressing an interest in trial participation (*Figure 1*). Twenty-nine of the 119 eligible practices expressed an interest in participating in the trial, giving a recruitment rate of 24% [29/119, 95% confidence interval (CI) 17 to 33]. We did not, however, continue the recruitment process in the remaining 90 practices as we had exceeded the

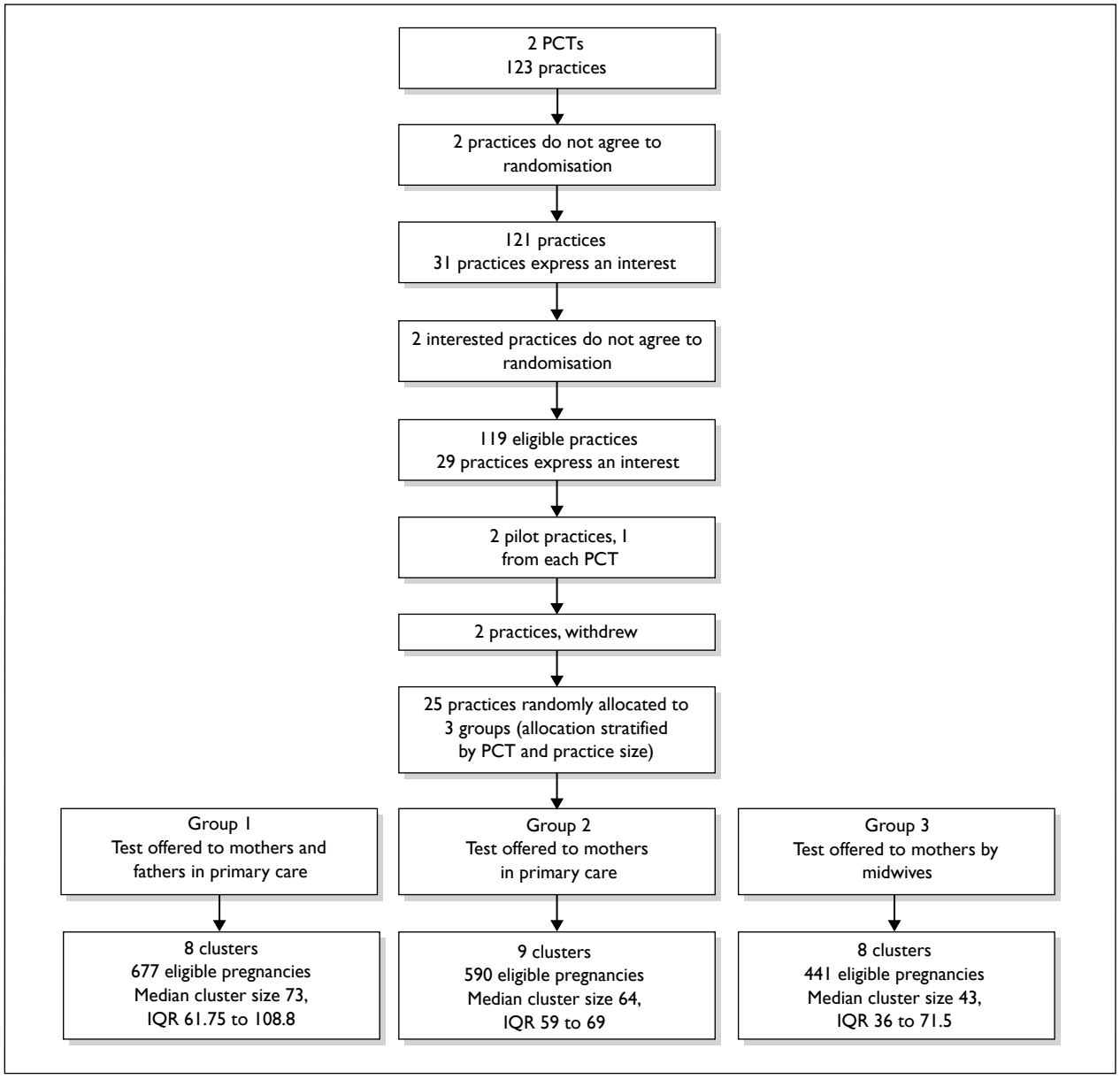


***FIGURE 1*** *Flow diagram of practices in the trial.*

target number of practices ($n = 24$). We have not speculated on how many additional practices would have participated in the trial if we had continued an active recruitment policy. Therefore, the recruitment rate of general practices to the trial is at least 24%.

Twenty-seven practices participated in and completed the trial, two as pilot sites and 25 as trial sites (*Figure 1*). Thus, we retained 93% (95% CI 77 to 99) of practices in the trial. Two practices withdrew because of work pressures, one prior to the run-in data collection phase starting, and one after training was completed but before the intervention phase started.

Practices that completed the intervention phase did not differ from the other practices in the two PCTs with respect to number of GPs ($p = 0.64$); the list size per GP ($p = 0.99$); the Townsend score ($p = 0.69$) or the resident per cent of minority ethnic groups ($p = 0.80$) (*Table 1*).

## Trial recruitment and retention

Qualitative analysis of interviews identified two major themes that seemed important in GPs' decisions to take part in the trial (*Box 1*): perceived importance or the research topic and a general

***TABLE 1*** *Differences between participating and non participating practices*

| | Participating practices | Non-participating practices | *p*-value |
|---|---|---|---|
| *n* | 27 | 96 | |
| Single-handed practice (frequency, %) | 7 (29) | 34 (38) | 0.636 |
| List size per GP (median, IQR) | 1971 (1780 to 3201) | 2270 (1776 to 2805) | 0.989 |
| Townsend score (median, IQR) | 10.3 (9.7 to 13.4) | 11.2 (9.5 to 13.6) | 0.694 |
| Resident per cent ethnic minorities (median, IQR) | 49 (34 to 62) | 51 (36 to 69) | 0.795 |

***BOX 1*** *GP motivations for taking part in the trial*

***Clinical importance***

Because we see an awful lot of pregnant, I don't know how many pregnant people we do see but we have quite a young population. We are often seeing pregnant people, anything to improve care. You know we're quite a proactive practice anyway. (HCP026)

I think we thought it was a valuable project, basically, and we thought it was useful for the patients to have an increased awareness of sickle in pregnancy. We have a very high proportion of people from the relative ... the relevant ethnic minorities, so it seemed sensible for us to do it, and we're very aware of the burden of sickle cell disease in the community because we have a lot of black patients. (HCP023)

Mainly because we thought it was a good idea because our population we serve is a very ethnic mix and we see a lot of Afro-Caribbean, African patients and Middle Eastern patients as well so we thought it would be good for the women to find out early on what their status was. (HCP020)

***Interest in research***

Well, we always try to do lots of different things, we like to engage in a bit of research, a bit of audit, a bit of service provision, enhanced care sort of thing. So that's one of the reasons. I mean, I've had a bit of a research background as well. We get a lot of requests from.. for research, people doing their degrees and many times we do help out. (HCP009)

We are a research practice in a sense, we train registrars, we train medical students and I think if we feel that it's something that is worthwhile doing then we do and I think that's what we agreed after reading the initial letter. (HCP018)

We have been involved with other trials and we are the largest practice, and we felt it was probably going to be an important trial. (HCP017)

***Practical reasons***

Um ... we have a very mixed population and we have a phlebotomist on site, it's very easy for us to offer this to a patient and then they can quite easily get an appointment, it's not too much hassle for them. And we do see a lot of pregnant women, a lot ... I think it's just the population age that we have here – a lot of pregnant women. (HCP030)

***Not sure***

I can't remember, I don't have the original links. (HCP032)

I have no idea, I can't remember. (HCP008)

I don't think I was involved in the decision to get involved ... I think that was made while I was away so I don't know. Possibly financial. (HCP10)

interest in research. In addition, one GP cited practical reasons for participation, while other GPs were not sure why they took part and one speculated that it might be for financial reasons. The two practices that withdrew from the study cited time pressures as the reason. One practice withdrew before starting the trial citing general pressures in primary care at the time. The second practice withdrew after the training session because offering the test in primary care was perceived as too time consuming.

The research team synthesised the above findings into a list of factors that are potentially important in recruitment and retention (*Box 2*).

# Discussion

## Summary of main findings

The description in this paper shows it is possible to recruit and retain representative primary care practices to a clinical trial, even in very socially deprived areas. Whilst we are not able to estimate an overall recruitment rate, we have demonstrated that the participating practices were representative of the population being investigated.

We believe there were three key elements of the recruitment strategy that facilitated recruiting a representative sample of practices. First, the topic of the research was perceived as relevant and clinically important to the practices. The trial assessed methods of offering antenatal screening for sickle cell and thalassaemia and was run in two geographical areas where 6% of pregnant women carry a significant haemoglobin variant. The invitation was signed by a local practising GP and endorsed by the local PCT. RISPs specifically included information about how few women were offered timely SCT screening in each PCT, i.e. the problem was quantified for the local practice population. Second, the method of inviting practices to participate in the trial was clear and concise. Published methods for providing key information in a systematic format were used, incorporating a timely follow-up system. An additional factor in the invitation method that may have led to a representative recruitment was the issuing of invitations to all practices in the two PCTs, rather than just those perceived to be interested in research or the topic of the trial.[6] Third, an interest in research was identified by participating GPs as an important reason for joining the trial. However, not all participating GPs had previous experience of research.

The trial was able to pay for costs incurred by practices through participation, including the costs of time needed to attend for training. These costs were requested as part of the research grant. This approach is in keeping with the current NHS contract for GPs. GPs expect to be reimbursed for work which is outside of their core contractual obligations, and the research team considered it essential to provide payment for 'non-core' work at a realistic rate. We are not able to determine the relative importance of payment in recruitment and retention. Only one GP identified financial reward as a possible reason in participating in the trial. In keeping with this, an Australian study of GPs indicated that financial reward was the least important variable associated with interest in participating in research.[21] Similarly, a recent Cochrane review reported that reimbursement for time spent on recruitment was unrelated to recruitment.[22] Our impression for the current trial is that the schedule or payment is related to trial retention, as discussed below.

## Retention

In this case study, 93% (27/29) of the recruited practices successfully completed the trial. We consider there were three key elements in our retention strategy that facilitated this. First, good, clear communication links were established between the research team and the practices. This was maintained on a weekly basis, between a nominated member of the research team and the practice link person, to ensure that any potential problems were identified and resolved rapidly by both the research team and the practice. However, it is not possible to identify the exact components of the communication strategy that were salient to good retention. Second, the use of easy data collection procedures reduced the burden on practice staff. Computerised data collection procedures were linked to routine antenatal templates at all practices, thereby facilitating data provision and collection. Some practices preferred not to use computerised data collection procedures. They were given blank forms that were completed by hand and faxed to the research team. This tailoring of data collection procedures to practices seemed important in reducing the burden of the trial. Third, the payment method was likely to have been important. The use of Research Activity Agreements allowed expenses to be paid as soon as pre-set targets were achieved. For example, interviews with GPs from each intervention practice were required by the trial protocol, but some general practitioners found it difficult to schedule

these interviews. Payment by pre-set targets seemed to encourage GPs to find the time for interviews which otherwise might not have achieved sufficient priority. All three retention strategies were identified as important when working with the pilot sites, indicating the value of using pilot sites to test practical measures.

Recruiting and retaining general practices is an essential part of conducting clinical trials in primary care. Recruitment and retention of patients is also essential. The strategies used to recruit and retain patient participants in SHIFT are described elsewhere.[23]

### Comparison with existing literature

The results of this case study are in line with the limited research on recruitment of practices to clinical trials. Foy and colleagues[5] reported that clear research and organisational strategies facilitate recruitment of general practices. The literature on retention of practices in trials is more limited than that on practice recruitment. Successful recruitment of participants by GPs is associated with good trial organisation, along with simple documentation and trial procedures.[13] Assuming that recruitment of participants is a reasonable proxy measure of retention of practices, then the findings reported by Prout and colleagues are in line with the findings of this case study.

### Strengths and limitations

This paper describes a series of strategies to recruit and retain general practices in a primary-care-based clinical trial. While a retention rate of 93% is successful, it could be argued that a recruitment rate of 24% is less successful. This rate provided sufficient power to answer the research question, and was representative of the population as a whole, so from this point of view it can be considered successful.

Qualitative data was collected from GPs in the intervention practices but not the standard care practices. As practices were allocated randomly, there is no reason to suppose that practices randomised to intervention groups were different to those randomised to standard care. The case study method is limited because it is only possible to describe the outcome of a multicomponent approach rather than the relative contributions of the different components. For example, it is not known whether financial compensation is needed or the extent to which payment upon meeting pre-agreed targets is important in recruitment and retention in a trial. The case study method does, however, act as a basis to formulate hypotheses about the most effective ways of recruiting and retaining general practices in primary care.

### Implications for future research

The hypotheses generated by this case study require testing in experimental studies. Some of the factors are more amenable to study than others. For example, it is possible to experimentally manipulate the invitation method and payment for participation or payment upon meeting pre-agreed targets. It is more challenging to develop an intervention assessing the importance of the research topic, or communication between practice and research team, or data collection methods, not least because it will be more difficult to maintain equipoise in these groups. Lack of equipoise has been shown to lead to poor retention in a trial.[12]

## Conclusion

Three factors appeared important in recruiting practices: the research topic, invitation method and interest in research. Three factors appeared important in retaining practices: good communication between practice and researchers, easy data collection methods and payment upon meeting pre-agreed targets. The effectiveness of these factors in facilitating recruitment and retention requires assessment in experimental studies.

## Acknowledgements

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## Competing interests

The authors have no competing interest to disclose.

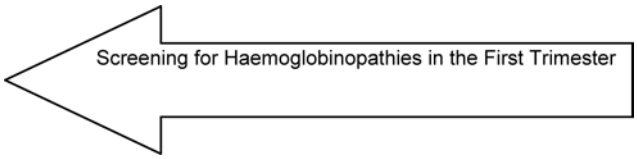
## Ethical approval

Ethical approval was granted to collect anonymised data on all pregnancies reported in participating practices (05/Q0501/36).

***BOX 2*** *Possible factors associated with recruitment and retention of general practices in a research trial*

| | |
|---|---|
| ***Recruitment*** | |
| Research topic | Perceived by GPs as relevant and important |
| Invitation method | Key information for practices is presented in a systematic format |
| | All practices in each PCT are invited to take part |
| | Telephone follow-up within 2 weeks of invitation |
| | Trial manager visited each practice interested in participating in trial |
| Costs to support research process | Costs incurred by the practice through participation are met, including any time needed to attend for training |
| Research | Interest and experience of research |
| ***Retention*** | |
| Clear communication to facilitate adherence to research protocol | A contact person for the research is identified within each practice |
| | Regular feedback is provided to the practice and any problems identified early and solutions generated jointly |
| | Training sessions on the trial protocol held at each practice |
| Easy data collection methods | Piloting of trial protocol |
| | Use of computer template linked to antenatal templates |
| | Participant packs for every pregnant woman |
| Payment schedule | Research Activity Agreements signed by the practice and research team specifying that money is paid as targets are achieved |

# Appendix I – Research Information Sheet for Practices (RISP) and invitation letter




## SHIFT (Screening for Haemoglobinopathies In First Trimester) Trial

***Purpose***

- **I.** To examine the feasibility, acceptability and effectiveness of offering antenatal screening for sickle cell and thalassaemia in one of three ways:

  – ***Group 1*** In primary care, when women first report their pregnancies with partners offered testing at the same time.
  – ***Group 2*** In primary care, when women first report their pregnancies with partners offered testing later and only if women are identified as carriers.
  – ***Group 3*** In community-based secondary care, when women are booked by midwives, with partners offered testing later and only if women are identified as carriers.

  – Practices will be randomised to offer screening in one way only.

- **II.** To model the cost-effectiveness of these three methods of offering screening.

**Context**
Many women are not making informed choices about antenatal screening for sickle cell and thalassaemia because they are not offered the test or they are offered the test too late in pregnancy. For example, in a recent audit in Newham in 2002, 59 couples were at risk of having an affected baby, but only nine had been screened by 11 weeks' gestation.

***Practice involvement (details overleaf)***
The practice will:

1. offer antenatal screening for sickle cell and thalassaemia to all pregnant women when the pregnancy is first confirmed, and
2. provide anonymous data on the number of pregnancies and time of offer and uptake of antenatal screening for sickle cell and thalassaemia.

**Ethical committee approval**
Ethical and R&D approval for the Trial has been obtained.

***Period of data collection***
Six months, plus retrospective data on number of pregnancies and time of screening for 6 months prior to data collection period.

***Suggested start date in this practice***
March 2006.

***Practice costs are reimbursed***
Yes, approximately £3000. This covers administrative costs of providing anonymised data, costs of offering the screening test to pregnant women and locum costs for attending a training session.

**Your project contacts:**

*Name*: Elizabeth Dormandy, SHIFT Trial Manager

*Phone*: 020 0000 0000

*Email*: elizabeth.dormandy@kcl.ac.uk

*Lead researcher*: Professor Theresa Marteau, Professor of Health Psychology

*Host institution*: King's College London

*Funder*: NHS R&D Health Technology Assessment programme

***Details of practice involvement***
**What the researcher will do**

- Provide nationally approved training in offering antenatal screening for sickle cell and thalassaemia and information for pregnant women and their partners about the screening process.
- Seek consent from women to take part in the evaluation of the trial.
- Conduct trial evaluations.
- Maintain contact with local midwives, counsellors, laboratory staff and obstetricians.

**To undertake the research the researcher will request access to the following personnel, records and/or practice facilities**

- Anonymised data on the number of pregnancies and the offer and time of screening for all pregnant women for a 12-month period (6 months prior to data collection and during the data collection period).
- Contact details of pregnant women who agree to be contacted by a researcher.

**What the practice personnel will be asked to do**

- Agree to randomisation to one of three patterns of care.
- Every GP to attend a training session in (1) offering antenatal screening for sickle cell and thalassaemia (2) the trial protocol (approximately 2 hours, provided at the practice).
- Provide data on the number of pregnancies and the offer and time of screening uptake for all pregnant women for a 12-month period.
- Offer screening to all eligible women for 6 months of the data collection period. Eligible women are those confirming pregnancy, aged 18 and over, wanting to proceed with the pregnancy and whose carrier status is not documented in primary CARE records. Practices randomised to Group 1 to offer screening to partners of eligible women.
- Seek permission for a researcher to contact pregnant women. One GP from each practice to participate in an interview about the experiences of offering screening in primary care.

Local sickle cell and thalassaemia counsellors will provide the support pathway for any carriers that are identified through SHIFT.

**How consent and confidentiality will be handled**

- The proposed research will be conducted in accord with the Research Governance Framework, COREC, LREC and PCT approvals.
- A researcher will only approach women who agree to be contacted. Women will be informed about the risks and benefits of study participation before consent to participate in the evaluation is sought.

**Practice feedback**

This will be provided by personal contacts with Elizabeth Dormandy and trial updates via SHIFT website. Feedback of results prior to presentation to the scientific community will be offered to practices either as a seminar held at the practice or a written report in the summer of 2007.

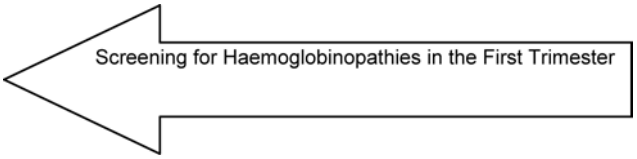
***We thank you for your help and interest.***

Please contact Elizabeth Dormandy if you would like any further information or clarification (email elizabeth.dormandy@kcl.ac.uk or tel. 020 0000 0000).

This Research Information Sheet for Practices was initiated by the General Practice & Primary Care Research Unit, Cambridge University.

Version 1.3: October 2005

email: elizabeth.dormandy@kcl.ac.uk




5th November 2004

Dear Dr

**SHIFT** – **S**creening for **H**aemoglobinopathies **I**n the **F**irst **T**rimester

We are writing to invite your practice to participate in a NHS R&D-funded study that aims to find the most effective way of offering antenatal screening for sickle cell and thalassaemia as early as possible. The study is being conducted in Lambeth and Newham and has the full backing of both PCTs.

Changing demographics means that the number of affected pregnancies affected by sickle cell and thalassaemia is increasing: these are now the most common genetic condition in England and Wales. This is particularly evident in Lambeth and Newham, where those at high risk for these conditions form a majority of the population. To date, screening services have served these populations poorly. For example, in a recent audit in Lambeth, Lewisham and Southwark fewer than half of the mothers of affected babies were offered PND. As well as being of practical clinical relevance, our study complements recent guidelines from NICE, the NSF for Children and Maternity Services, and the National Screening Programme for Sickle Cell and Thalassaemia.

We realise that you have many calls on your time and therefore propose funds to cover the costs. This has been estimated by local GPs to be about £3000 per practice. We will offer training to all practices to help them in the offer of screening and the practicalities of data collection. Benefits of participation include responding to a well-documented local need, as well as taking a lead locally and nationally and helping to shape future health policy. Details of what participation involves are included in the enclosed practice information sheet. Please note that data collection for the study will start in December 2005.

Elizabeth Dormandy, the Trial Manager, will be contacting your practice manager to discuss this in the next 2 weeks. If, in the interim, you have any questions do not hesitate to contact her.

Yours sincerely

T Marteau p.p. Richard Williams

Theresa Marteau,
Principal Investigator

Elizabeth Dormandy,
Trial Manager

Richard Williams
GP, Brixton Hill Group Practice

On behalf of the SHIFT Trial Team

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# Appendix 2
# Trial protocol

Abstract first published online in the *Lancet* 5 March 2008: www.thelancet.com/journals/lancet/misc/protocol/06PRT-921.

## Abstract

### Title

Protocol 06PRT/921: Antenatal screening for haemoglobinopathies in primary care: a cluster randomised trial to inform a simulation model. The Screening for Haemoglobinopathies in First Trimester (SHIFT) trial (ISRCTN00677850).

### Principal investigator

Professor Theresa Marteau, Health Psychology Section , King's College London, SE1 9RT, UK (tel. (0)20 7188 0192; fax: (0)20 7188 0195; email: theresa.marteau@kcl.ac.uk).

### Background

It is now UK policy to offer antenatal screening for haemoglobinopathies in a timely manner to all pregnant women in high-prevalence areas. There is, however, insufficient evidence to determine the most cost-effective way of delivering the service to achieve this goal.

### Aims

SHIFT has two aims. The first aim is to assess and compare the feasibility, acceptability and effectiveness of offering antenatal screening for sickle cell disease and thalassaemia (haemoglobinopathies) in one of three ways: Group 1 – in primary care, when women first report their pregnancies with parallel father testing (i.e. the baby's father is offered screening at the same time as the pregnant woman); Group 2 – in primary care, when women first report their pregnancies with sequential father testing (i.e. the baby's father is only offered screening if the pregnant woman is found to be a carrier); and Group 3 – in community-based secondary care, when women are booked by midwives with sequential father testing.

The second aim is to model the cost-effectiveness of these three different ways of offering screening to parents.

### Design

SHIFT is a partial factorial cluster-randomised trial. General (family) practices will be randomised to one of the three groups above, and pregnant women will be offered screening according to the group to which the practice at which they are registered has been randomised. There will be 24 general practices from two primary care trusts in London: Newham and Lambeth.

#### *Target populations*

- All pregnant women receiving antenatal care in the study settings, wanting to proceed with the pregnancy, and whose carrier status is not documented in their primary care records.
- Fathers of babies of eligible women randomised to Group 1.
- Health professionals providing antenatal care to eligible parents.

#### *Outcomes*

*Primary outcomes* The primary effectiveness outcome measures are the gestational age that antenatal screening for sickle cell and thalassaemia is done and the gestational age that such screening is offered.

*Secondary outcomes* Effectiveness will also be assessed by quantitative measures of informed choice. Feasibility and acceptability will be assessed by semistructured interviews with general practitioners and women. Acceptability for women will also be assessed by quantitative measures that examine the emotional response to carrier testing and concern about results. Costs to women and the health service will be assessed by collecting data on resource use for observed short-term events, including screening and counselling carrier couples.

#### *Simulation model*

Outcome data will be used to inform a new simulation model, developed from an existing and

published sickle cell and thalassaemia screening model. The simulation model will be used to predict longer-term antenatal screening outcomes, such as miscarriage, after prenatal testing. The model will be used to explore the incremental costs and effectiveness of the alternative screening approaches.

***Sample size***

The primary outcome will be collected on 792 women, which gives sufficient power to detect an increase from 30% to 50% of women offered screening by 10 weeks' gestation in primary versus community-based secondary care, with 90% power at the 5% level of significance, assuming an intraclass correlation coefficient of 0.03. Rates of informed choice will also be determined for these women.

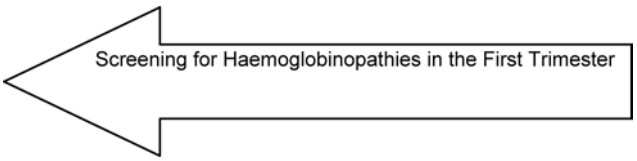
***Analysis plan***

We shall compare the relative odds of a woman achieving three outcomes (uptake of screening, uptake of screening by 10 weeks, and the making of an informed choice) in Groups 1 and 2 versus Group 3, and the relative odds of women knowing their baby's father's carrier status as well as their own by 11 weeks in Groups 1 versus 2. We shall adjust for confounding variables, including age, parity, ethnicity, education, and other indices of socioeconomic status. We will use regression methods for clustered data to estimate odds ratios and their confidence intervals after adjusting for confounders and clustering by care provider.

***Sponsor***

NHS R&D Health Technology Assessment programme.

*Date trial started*: January 2006
*Expected end date*: October 2007
*Expected reporting date*: December 2007




# SHIFT Trial protocol

Version 3.0 (without appendices) 23 February 2007. Changes to protocol listed at end of this appendix.

## Title

Antenatal screening for haemoglobinopathies in primary care: a cluster randomised trial to inform a simulation model. The Screening for Haemoglobinopathies in First Trimester (SHIFT) trial.

## Abstract


### *Background*

It is now UK policy to offer antenatal screening for haemoglobinopathies in a timely manner to all pregnant women in high-prevalence areas. There is, however, insufficient evidence to determine the most cost-effective way of delivering the service to achieve this.

#### *Objectives*

- To assess and compare the feasibility, acceptability and effectiveness of offering antenatal screening for sickle cell and thalassaemia (haemoglobinopathies) in one of three ways:
  - *Group 1* In primary care, when women first report their pregnancies, with parallel father testing (i.e. the baby's father is offered screening at the same time as the pregnant woman).
  - *Group 2* In primary care, when women first report their pregnancies, with sequential father testing; (i.e. the baby's father is only offered screening if the pregnant woman is found to be a carrier).
  - *Group 3* In community-based secondary care, when women are booked by midwives, with sequential father testing.
- To model the cost-effectiveness of these three different ways of offering screening to parents.

#### *Design*

A partial factorial cluster randomised controlled trial of screening will be used to compare three methods of offering antenatal sickle cell and thalassaemia screening, and to model the cost-effectiveness of each method. General practices will be randomised to one of three groups, and pregnant women will be allocated to according to the practice at which they are registered:

- *Group 1* In primary care, when women first report their pregnancies, with parallel father testing.
- *Group 2* In primary care, when women first report their pregnancies, with sequential father testing.
- *Group 3* In community-based secondary care, when women are booked by midwives, with sequential father testing.

#### *Setting*

Twenty-four general practices will be recruited from two primary care trusts, Newham and Lambeth, where 61% and 49% of the population, respectively, are from minority ethnic groups.

#### *Target population*

- All pregnant women receiving antenatal care in the study settings, who are aged 18 and over, wanting to proceed with the pregnancy, and whose carrier status is not documented in primary care records.
- Fathers of babies of eligible women randomised to Group 1.
- Health professionals providing antenatal care to eligible parents.

#### *Costs*

Data on resource use will be collected for observed short-term events, including screening and counselling carrier couples. The resource implications associated with rarer events (e.g. miscarriage following prenatal diagnostic testing) will be estimated using a simulation model.

#### *Outcome measures*

- Time of screening.
- Offer of screening.
- Time when women know the carrier status of the baby's father.
- Rates of informed choice.
- Couples' emotional responses to carrier testing, assessed using both quantitative and qualitative methods. The feasibility and organisational impact of offering screening in primary care

will be assessed using interviews with couples and relevant health-care professionals involved in sickle cell and thalassaemia screening in primary care.

#### *Sample size*

The main outcome will be collected on 792 women receiving care in 24 general practices in two PCTs. This gives sufficient power to detect an increase from 30% to 50% of women offered screening by 10 weeks' gestation in primary versus community-based secondary care, with 90% power at the 5% level of significance, assuming an ICC of 0.03. Rates of informed choice will also be determined for these women.

#### *Project timetable*

Thirty-six months (October 2004–September 2007).

#### *Funding body*

NHS R&D National Coordinating Centre for Health Technology Assessment.

## SHIFT protocol

### *Research objectives*

**Objective I**

To assess and compare the feasibility, acceptability and effectiveness of three ways of offering universal antenatal sickle cell and thalassaemia (SCT) screening:

- *Group 1:* In primary care, when women first report their pregnancies with parallel father testing (i.e. the baby's father is offered screening at the same time as the pregnant woman).
- *Group 2:* In primary care, when women first report their pregnancies with sequential father testing (i.e. the baby's father is only offered screening if the pregnant woman is found to be a carrier).
- *Group 3:* In community-based secondary care, when women are booked by midwives with sequential father testing.

**Objective II**

To model the cost-effectiveness of these three patterns of care, using the data collected as part of achieving Objective I.

### *Review of existing research*

**The problem**

Many at-risk pregnant women and the fathers of their baby are either not being offered SCT carrier tests or the process of screening and diagnostic testing is taking too long to allow couples the full ranges of reproductive options. These include prenatal diagnostic testing for carrier couples, and, where an affected pregnancy is identified, the offer of a termination. Given the recent statutory requirements to reduce disparities between ethnic and social groups in the provision of health care,[1] it is germane to consider how antenatal screening for SCT can be organised to minimise the failure to offer screening early in pregnancy, the basic premise upon which the policy of universal screening is based.[2]

**Screening policy**

Screening policy options for SCT in the UK were reviewed in two systematic reviews commissioned by the Health Technology Assessment (HTA) programme.[2,3] The results of these reviews informed the proposed introduction of a universal antenatal screening policy in areas of high prevalence by 2004.[4] Having introduced this policy, it is now important to determine how it is most effectively translated into practice to ensure not only that all at-risk pregnant women are offered screening, but also that this is done sufficiently early in pregnancy to allow women and babies' fathers the full range of reproductive options. It is the aim of the proposed research to assess the feasibility, acceptability and effectiveness in achieving earlier testing by offering screening in primary care at the time a woman first reports her pregnancy to her general practitioner.

**Current patterns of care**

Currently, screening is offered to pregnant women in a variety of settings, most often when they attend for a booking appointment with a midwife. The location of such appointments varies across the country: they may take place in hospital, in the woman's home or in a community-based clinic. The community-based clinic (which we have designated 'community-based secondary care') appears to be the most common pattern of screening in the UK, especially in Greater London, where about half of the UK minority ethnic population live.[5,6] We have therefore used this pattern of screening as the comparison against which screening in primary care will be judged.

**Informed choice**

As with other screening programmes, a central aim of the NHS Sickle Cell and Thalassaemia (SC&T) Screening Programme is to offer couples the opportunity to make an informed choice about participation in the screening programme.[4,7]

Research on the factors associated with informed choice for people making health-care decisions has tended to assess one dimension only, most often knowledge about a procedure.[8,9] It is now widely acknowledged that informed choice is more complex than this and involves several dimensions.[10,11] A consensus is emerging that informed choices have two core characteristics: first, they reflect an individual's values, and second, they are made in the context of good knowledge.[7,11–14] Building on this, we have developed, to our knowledge, the first operational definition of an informed choice: 'A decision based on relevant knowledge, consistent with the decision-maker's values and behaviourally implemented'.[15]

Thus, an informed choice to accept testing is one based on good knowledge, where those with positive attitudes towards undergoing the test have it; an informed choice to decline testing is one based on good knowledge, where those with negative attitudes towards undergoing the test do not have it. Choices based on poor knowledge or which are inconsistent with values are classified as uninformed.

## Lack of informed choice in the context of screening for SCT

Many factors have been identified as important in limiting the opportunity for couples to make informed choices in the context of antenatal screening for SCT.[16]

### *Failure to offer screening*

This can occur when women are incorrectly judged as having low risks of being carriers and hence are not offered the test. Non-northern European ethnicity has been used as a poor proxy measure of risk status for SCT, with misclassification occurring at a rate as high as 20%.[17] This reflects the practice of some health professionals offering screening on the basis of skin colour or family name.[18,19]

Failure to offer screening also follows erroneous assumptions by health professionals about women's attitudes towards undergoing the screening tests. For example, some health professionals assume that Asian women will not terminate pregnancies, and as a result do not offer screening tests to them.[20] In fact, existing evidence suggests that ethnicity is a very poor predictor of women's attitudes towards undergoing antenatal screening.[21,22]

The NHS SC&T Screening Programme has sought to address the failure to offer women screening by making it national policy for screening to be offered to all pregnant women in areas of high prevalence (the universal screening policy), facilitating this by instigating nationally co-ordinated education and training of health professionals.

### *Couples lack of knowledge about the screening test*

Making an informed choice requires potential participants of screening programmes to have good knowledge about the screening programme. Several surveys show poor knowledge of SCT and of antenatal screening for these conditions.[23–25]

The NHS SC&T Screening Programme has commissioned the development of information materials for screening participants (including those who do not speak or read English and those with low levels of literacy) and health professionals. These are being evaluated to help achieve high levels of knowledge in couples making choices about screening.

### *Diagnostic testing is offered too late in pregnancy*

The variation in uptake of prenatal diagnostic tests is associated with the time in pregnancy that the screening test is offered. For example, 73% of British Pakistani women accepted prenatal diagnosis for thalassaemia when it was offered in the first trimester compared with 39% when offered in the second trimester.[26] This may be a particular problem for women whose pregnancies are at risk for sickle cell disease, with one retrospective study reporting that the mean gestation at which women who were carriers for sickle cell were first seen for counselling was 15 weeks, compared with 12.3 weeks for women who were carriers for thalassaemia.[27]

There are several reasons why delays occur in couple's learning about their carrier status. Some laboratories produce screening test results within 48 hours,[28] whereas others take 5 days or more.[5] In addition, once results are known, it can take anything from 6–34 days for women to receive an appointment for counselling about diagnostic testing options.[29] Thus, the speed at which laboratories process samples and report screening results can limit couples' opportunities to make informed choices.

The NHS SC&T Screening Programme has set standards for the time taken for laboratories to report a result (three working days[4]) and for the time interval between informing women of their carrier status and offering an appointment for a

consultation to discuss diagnostic testing options (5 working days).

**Reducing delays in the screening process: the proposed study**

We propose to assess two ways of delivering antenatal screening for SCT that have the potential to reduce delays in the screening process: (1) offering screening at the time when women first report their pregnancies in primary care and (2) offering testing to the baby's father at the same time as pregnant women are offered screening.

***Time in pregnancy when screening is offered***

Antenatal care is most often initiated when a woman reports her pregnancy to her GP, who then refers the pregnant woman to a community midwife to 'book' her for antenatal and maternity care. Screening is usually offered at this midwifery booking appointment, which commonly occurs between two and four weeks later, with some women not having this until 15 weeks' gestation,[30] many weeks after reporting their pregnancies to their GPs. The delay between reporting a pregnancy and seeing a midwife can be greater for women from ethnic minorities. General practitioners tend to book South Asian women later than other women, despite these women reporting their pregnancies at similar gestations to other women.[31,32] The extent and possible causes of these delays are not known.

Offering antenatal screening for SCT when women first report their pregnancies to their GPs has the potential to reduce this delay, a solution recognised in the recent NICE guidelines on maternity care[33] and National Service Framework on Maternal and Child Health.[34] Such an approach to offering carrier testing in primary care for another recessively inherited condition, cystic fibrosis, was successfully conducted by one of our team in Manchester.[35] The extent to which this approach is feasible, acceptable and effective in the different cultural context of SCT is unknown. While offering screening at the earliest opportunity, *i.e.* as women report their pregnancies, has high face validity as a way of ensuring a timely offer and uptake of screening, offering screening at this time may be less effective at achieving informed choice than an offer made by a midwife as part of a longer booking appointment. We shall evaluate this and other outcomes in the proposed study.

The proposed study will address the two main problems identified in two recent pilot studies offering antenatal screening for SCT in primary care.[28,36] The first problem concerned low levels of knowledge in couples.[28] The authors called for better information for those offered screening and training of health-care professionals (HCPs), all of which will be incorporated in our proposed study. The second main problem concerned the failure to provide primary care practices with the resources needed to provide the screening service.[36] All of the HCPs included in our proposed study will receive training in collaboration with PEGASUS (Professional Education for Genetic Assessment and Screening), the nationally co-ordinated health professional training programme. Participating practices will receive NHS costs to cover the offer of SCT screening according to the study protocol, research costs for providing anonymised data on the number of pregnancies, time and uptake of testing, and costs to provide locum cover when GPs are trained in both offering antenatal SCT screening and study protocol.

***Stage in the screening process when fathers are offered screening***

Even if women are offered screening early in pregnancy, much time may elapse in offering testing to the baby's father, which delays couples knowing their joint carrier status. Sequential testing is the usual pattern of care offered in SCT testing. In one study male partners were offered screening up to 4 weeks after their female carrier partners.[30] In cystic fibrosis screening, father testing has been conducted in one of two ways: *parallel father testing*, in which samples are taken and tested from both parents at the same time, and *sequential testing*, in which blood is taken from the father only after the woman has been tested and found to be a carrier.[37]

While parallel father testing has the potential to provide couples with information on their carrier status earlier than sequential testing, it is not known how feasible, acceptable or effective it is in the population at highest risk of SCT. The project is being implemented in deprived inner city areas, where the population is characterised by high mobility, low income and low education. This may lead to difficulties if few women attend with their baby's father, if fathers are not registered with the same GP or if fathers are not resident in the UK.[17] Estimates of partners attending for sickle cell testing after women have been identified as carriers vary between 63% and 81%.[2,27] Many of these characteristics pose problems for sequential as well as parallel father testing, including the suspicion and fear of stigmatisation that some men feel regarding carrier testing.[38] To ascertain whether

parallel father testing is a viable model, we propose to evaluate how feasible, acceptable and effective it is in bringing forward the time at which couples who want screening can know their joint carrier status. We propose to evaluate this method of offering father testing in primary care only, as this is the most likely pattern of care to result in earlier knowledge of couple carrier status.

**Future patterns of care**

It is likely that as the NHS SC&T Screening Programme becomes established and the community becomes familiar with it, so the ways in which screening will be conducted will change. Thus, the experience of one of us (Dr Jane Logan) is that as a community served by a general practice routinely incorporates carrier screening for SCT into care, so carrier testing is more likely to take place before pregnancy. There will, however, always be a need to run several models of care of which the early offer of screening in pregnancy will be an important one.[39] It is unclear whether this is best conducted by a GP, a practice nurse or a midwife. Discussions with members of primary care teams suggest that the pattern we propose is, given the way care is currently organised, the most feasible way of delivering an early offer of screening.

### *The proposed study*

**Research methods**

For the study to inform national policy it requires a robust design with appropriate outcome measures, as well as data collection methods that will minimise the biases that arise from missing data.

***Study design***

A partial factor cluster randomised controlled trial, with general practice as the unit of randomisation, will be used to evaluate first, screening offered in primary care at the time women report their pregnancies, and, second, father testing offered at this same time. It has a partial factorial design as we have chosen to evaluate parallel father testing only in primary care, to determine the extent to which this approach to father testing can build upon offering testing to women in primary care to achieve the earliest possible time at which couples can know their carrier status.

***Outcome measures***

We have chosen the timely conduct of screening for SCT as the main outcome measure. This is a necessary first outcome in ensuring that carrier couples learn of their carrier status in sufficient time to select, if they so choose, prenatal diagnostic testing and, if appropriate, termination of affected pregnancies. It is also the outcome measure that allows for robust appropriately powered studies to be designed within a realistic time frame. By using test uptake as the primary end point for the proposed studies we do not consider uptake *per se* to be a desirable outcome of the offer of screening: uptake in the absence of informed choice is, in the view of the Human Genetics Commission and similar other bodies, an undesirable outcome. Therefore, we propose to assess the time of offer of screening and the extent to which choices in the patterns of care being studied are informed. To our knowledge we propose the first systematic assessment of the extent to which fathers' choices are informed.[15] Other outcomes, such as the offer of prenatal diagnostic testing, miscarriage rates, and the numbers of affected and unaffected births require data collection from the whole of England for more than 1 year to have sufficient power to examine the effectiveness of different patterns of care, given the estimated annual number of affected conceptions in England (28–60 for thalassaemia and 133–238 for sickle cell[2,3]). The NHS SC&T Screening Programme will be able to assess these outcomes when a nationally co-ordinated IT system of data collection is in place. In the interim, we propose to collect data regarding the performance of different patterns of care in the initial stages of the screening process, while modelling outcomes for the latter stages, in which significant outcomes are rarer.

***Minimising missing data***

We aim to minimise this potential bias of missing data in two ways:

1. *Maximising study participation across all ethnic groups* Consumers will be actively involved at all stages of planning the study, including data collection, so that the cultural sensitivities of the local consumers are addressed. This will ensure, as far as possible, that a representative sample and response rate is achieved. All study materials will be available in translation, in writing and on audiotape. In addition, we aim to recruit researchers who can speak one or more of the main Asian and African languages spoken by women invited to participate in the study.
2. *Obtaining the main outcome measure on all pregnant women* The main outcome measure, the time of offer and uptake of screening, will be obtained using anonymised data from the participating general practices for all pregnant women reporting their pregnancies during the 6-month period of data collection. We do not

anticipate any selection bias with this method as records from all eligible women will be included.

***Research setting***

The study will take place in two PCTs, Lambeth and Newham, covering areas with high prevalence of Black African, Black Caribbean, Indian, Pakistani and Bangladeshi and mixed-heritage women. This sample reflects ethnic and cultural diversity, as well as a variety of socioeconomic backgrounds. The sample is likely to detect an equal mix of couples at risk from SCT. The estimated ethnic composition in the two areas, based on 2001 Census data, is given in *Table 1*,[40] along with the main languages spoken apart from English.

Earlier research into women's experiences of thalassaemia screening has failed due to communication failure between HCPs.[19] We have sought to address this problem at an early stage in the research process by establishing collaborative links with the key stakeholders involved in the provision of antenatal screening for SCT. These include representatives from the two PCTs, as well as the sickle cell and thalassaemia centres, midwifery and obstetric leads, and haematology laboratories in the two PCTS.

We have identified 33 practices (19 from Lambeth PCT and 14 from Newham PCT) that have expressed an interest in participating in SHIFT. We feel this positive response reflects the recognised importance of the problem and the desire of many primary care professionals to participate in an adequately resourced research study. Participating practices will receive high-quality training to provide a service they perceive to be of great value to their patients.

***Training health-care professionals***

The NHS SC&T Screening Programme has commissioned a training programme, PEGASUS, led by Professor Joe Kai, to develop and implement training for HCPs working in primary and secondary care. We shall work with Professor Kai to implement this in the context of the trial (see appendix I).

***Objective 1***

To assess the feasibility, acceptability and effectiveness of offering universal antenatal SCT screening in three ways:

- *Group 1 – in primary care, when women first report their pregnancies with parallel father testing (i.e. the baby's father is offered screening at the same time as the pregnant woman)* Women will be offered screening for SCT when they first report their pregnancies to their GPs, the first opportunity to offer SCT screening in pregnancy. A verbal explanation of the test will be supplemented by written information, prepared for the NHS SC&T Screening Programme (see appendix II). Women wishing to be tested at that time will have blood taken using the usual procedure for phlebotomy at the practice. Those wanting more time to decide will be invited to return within 1 week. Fathers of babies of women receiving care from general practices in this study group will be offered parallel father testing, i.e. fathers are offered testing at the same time as the woman. If the father is present when a woman first reports her pregnancy to the GP, the test will be offered by the GP at this time. If the father does not attend this visit, the woman will be invited to offer the opportunity for her baby's father to be tested, using a take-home

***TABLE 1*** *Estimated ethnic composition from study sites*

| | Lambeth | Newham |
|---|---|---|
| Black Caribbean | 11.8 | 7.3 |
| Black African | 17.5 | 13.1 |
| Black other | 6.7 | 1.1 |
| Indian | 1.4 | 12.1 |
| Pakistani | 0.7 | 8.5 |
| Bangladeshi | 1.0 | 8.8 |
| Other | 9.6 | 9.7 |
| Northern European | 51.3 | 39.4 |
| Main languages spoken (listed alphabetically) | Eritrean French, Hindi, Lingala, Portuguese, Spanish and Urdu | Bengali, French, Lingala, Lunganda, Punjabi and Urdu |

pack (see appendix III). The pack contains information about the test, details of several local places (primary care, local hospital, SCT centre) where this can be undergone, and a completed request form that identifies both parents and provides the address of the father's GP for reporting results. Fathers' samples will be analysed upon receipt in the laboratory, in parallel with women's samples. Follow-up of women identified as carriers will be led by local SCT counsellors, in line with the NHS SC&T Screening Programme protocol.

- *Group 2 – in primary care, when women first report their pregnancies with sequential father testing (i.e. the baby's father is only offered screening if the pregnant woman is found to be a carrier)* Women will be offered screening for SCT when they first report their pregnancies to their GPs, as in Group 1. Fathers of babies of women receiving care from general practices in this study group will be offered sequential testing, i.e. offered testing only if the woman is found to be a carrier for sickle cell or thalassaemia. The offer of testing to fathers of babies of women identified as carriers will be made by local SCT counsellors, in keeping with the NHS SC&T Screening Programme protocol.
- *Group 3 – in community-based secondary care, when women are booked by midwives with sequential father testing* When women first report their pregnancies to their GPs, they are referred to a community midwife to be 'booked' for antenatal and maternity care. The midwife offers antenatal SCT screening at this booking visit, which can be conducted at the woman's home, in a community-based clinic or at a hospital. The fathers of babies of women receiving care in practices in this study group will be offered sequential testing, as described above. This is currently standard care in Lambeth and Newham PCTs.

## Design

The design is a partial factorial cluster randomised controlled trial in which 24 general practices consenting to participate in the study will be allocated to one of three groups (*Figure 1*).

## Outcome measures

### *Effectiveness*

In addition to cost-effectiveness (see Objective II), three other aspects of effectiveness will be assessed:

1. *Time of uptake of screening (primary outcome)* These data will be collected in two ways to ensure completeness of data collection:
   i. GP databases – from these, GPs will provide anonymised data on the number of pregnant women who are tested for SCT and the time in pregnancy when the woman was tested. These data will be provided for the 6 months before the study commences, as well as the 6 months' period of data collection in each practice.

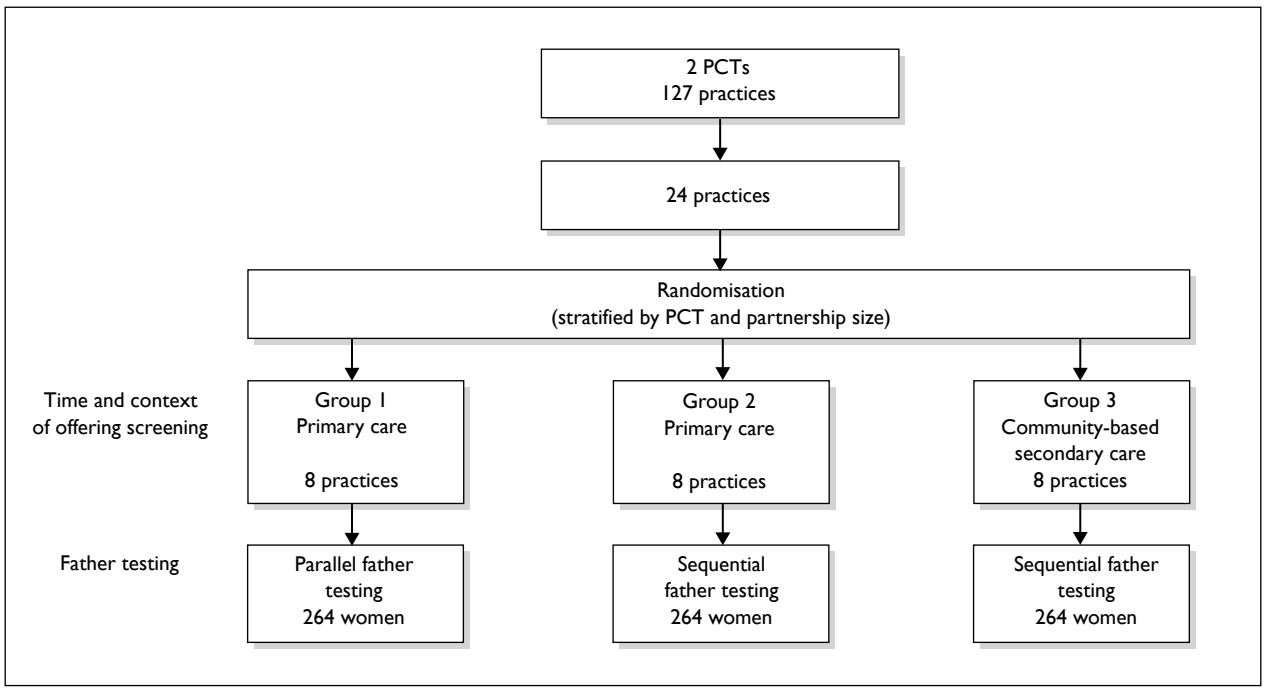



***FIGURE 1*** *Study design.*

As these data are anonymised we do not need to obtain individual patient consent or apply for exemption under Section 60 of the Health and Social Care Act (2001).[41]

ii. Women participating in the quantitative and qualitative components of the study will be asked to give permission for information on testing to be taken from their laboratory and maternity notes.

2. *Time of offer of screening* This will be collected in the same way as time of uptake of screening.
3. *Time at which women know there babies fathers' carrier status* The ideal outcome is the proportion of carrier couples that know their carrier status by 11 weeks. To power the study using this outcome measure would require UK-wide data. For the study to be feasible we have powered it using the proportion of women who know the carrier status of their babies' fathers by 11 weeks.

***Informed choice about screening***

This will be measured for participants who accept or decline screening, using our standardised measure, comprising a multiple-choice measure of knowledge about the screening test and a measure of attitudes towards undergoing the screening test.[15,42] Choices are classified as 'informed' in individuals with high levels of knowledge (above the mid-point) and who act in line with their attitudes, i.e. those with negative attitudes do not have the test, while those with positive attitudes do have the test. We have good evidence of its validity in assessing informed choice in the context of antenatal screening.[15,42–45]

***Acceptability***

This will be assessed in two ways:

- Women's and the babies' fathers' emotional responses to carrier testing This will be assessed using two questionnaire-based measures:
  - An adjective checklist, found to discriminate between carriers and non-carriers of autosomal conditions.[46]
  - A two-item measure assessing concern about test results, a measure that we have found sensitive when assessing women's responses to other screening tests.[47]
- Semi-structured face-to-face interviews from a sample of women and men, to ascertain their experiences of:
  - the offer of antenatal screening for SCT
  - deciding whether to accept the offer
  - for those accepting the offer, their experiences of the process of screening
  - for those declining the offer, their experiences of this.

Participants will be asked to consent to a possible interview at a place of their choice after the testing process. Approximately 20 women and, if consenting, their babies' fathers will be asked to complete an interview. A semistructured interview schedule and questionnaire will be used to elicit women's and fathers' experiences, as listed in the aims above (see appendix IV, Interview schedule). For people who do not speak English these interviews will be conducted in a language of their choice, using either research staff or interpretation services. The interviews will be tape recorded and transcribed. The analysis of these interviews will draw on grounded theory using the method of constant comparison. The software package ATLAS-TI will be used to organise the transcripts. A provisional, inductive coding frame will be derived from the earlier stages of the analysis but will be modified as new themes emerge. This will be used to assign codes to the transcribed data. The data in each category will be summarised and themes identified and developed. Simultaneous sampling and analysis will continue until all categories are saturated and no new information is forthcoming. This component of the study will be led by Professor Michael Calnan and Dr Karl Atkin.

***Feasibility***

This will be assessed using semistructured face-to-face interviews with participating GPs, midwives, practice nurses and counsellors. The interviews will focus upon identifying obstacles and ways of removing these.

Participants will be identified using a purposive sampling frame of key informants (GPs and midwives) from the participating practices including, if possible, at least one informant from each practice. Interviews will be tape recorded and carried out or supervised by an experienced qualitative, primary care researcher (Professor Michael Calnan). The themes explored in the interview will depend on the role of the informant, but the general themes will involve their experiences of offering the test; the obstacles and enabling factors, and how any obstacles were or could have been overcome; and descriptions of the training and the extent to which they felt it met their needs. The analysis of these interviews will draw on grounded theory using the method of constant comparison as described above. For details of the interview schedule, see appendix V.

***Other measures***

*Ethnicity* Women will be asked to provide information on their ethnicity and that of their babies' fathers, with question wording from the Health Survey of England:

- *Socioeconomic status* Women will be asked to complete a simple three-item measure based on educational qualifications, car ownership and home ownership to assess socioeconomic status.[48]
- *Parity Details* will be collected from the women.
- *Knowledge of sickle cell and thalassaemia carrier status* Knowledge at the time of reporting pregnancies or booking appointment will be recorded.
- *Reproductive decisions* Information will also be collected on any choices that carrier women and carrier couples make regarding diagnostic testing and pregnancy termination and their satisfaction with the decision.
- *Direct access to midwifery care* Midwives offering antenatal care to women in the trial will be asked to record the number of women who access midwifery care without a referral from their GP. For these women, midwives will be asked to record the offer of screening and time of screening, and ask if a researcher can contact the women.

The involvement of practice nurses in offering antenatal SCT screening will be recorded for Group 1 and 2 practices. See Appendices 6 and 7, respectively, for details of the Time One and Two questionnaires.

**Study samples**

***Health-care professionals***

The study sample will comprise general practitioners and midwives providing antenatal care to pregnant women in the 24 participating general practices in two PCTs.

- *Women* Eligible pregnant women attending participating practices who wish to continue with the pregnancy, are less than 19 weeks 6 days' gestation at their first visit to the GP in this pregnancy, and who have no written record of SCT carrier status in primary care. All participants offered the test aged 18 or over are eligible to complete the questionnaire.
- *Fathers* Those eligible for the study are fathers of babies of women in Group 1.

***Proposed sample size***

We estimate that we require data on the main dependent variable for 792 women attending 24 general practices (33 women per practice) (see *Figure 1*). This gives sufficient power to detect a difference of 20% in the proportion of women undergoing screening by 10 weeks' gestation in different settings. In a sample of pregnant women in South Thames, 30% were screened by 10 week[32] and the proportion is predicted to be 50% when screening is offered in primary care. We have assumed 90% power at the 5% level of significance and an intraclass correlation coefficient (ICC) of 0.03. This ICC estimate is based on data from 31 studies in primary care, in which 75% of ICCs were less than 0.032.[49] In order to detect a difference between 30% and 50% under simple random allocation, 134 participants per group would be required. To allow for cluster randomisation this must be appropriately inflated (eq2 of Campbell[50]), giving a requirement for 33 participants per practice and with eight practices per group there will be 264 women per group in total. This gives at least the same power (> 90%) to detect an difference in the proportion of women knowing their babies' fathers' carrier status from an estimated 10% to 30%, predicted to occur with parallel father testing (Group 1) compared with sequential father testing (Group 2). Adjustment of analyses for sociodemographic confounders and baseline screening performance should enhance the precision of estimated differences in screening outcomes between settings. A recruitment rate of 33 eligible women in a 6-month period is feasible, given the reported 100–150 pregnancies per year in the general practices wishing to participate in the study. Even if we lost one practice from each group, leaving seven, then the required recruitment would be feasible in the study time period (42 women from each of the remaining practices). Questionnaire based data will be collected from 232 women in each of the three study groups (including fathers of babies of 232 women in Group 1, the only group in which fathers are routinely offered the test), which allows an estimate of the proportions making an informed choice in each group within 10%, with 95% confidence, allowing for clustering.

**Procedure**

All general practices in the two PCTs have been contacted and invited to participate in the study. Eligible practices are those that have a computerised database with means of providing anonymised data on the number of pregnancies, time of offer of screening, and time of uptake for those women who accept testing and who agree to be randomised. Twenty-four of these will be randomised to the trial arms, and stratified by PCT and partnership size. Training in collaboration with

PEGASUS will be arranged for all participating health professionals in these practices, as described above. The research team will train these health professionals in the research protocol and maintain close links with the participating practices to ensure fidelity to the protocol (see page 15 for Quality Assurance procedures). Practices in Group Three will be offered training after the recruitment period. Data collection will last for 7 months in each general practice, and commencement of data collection will be staggered at a rate of three practices per month for the first 8 months of the data collection phase.

General practitioners will offer SCT screening using the usual procedures for consent for antenatal blood tests, using information materials developed by the National programme. Midwives in the participating practices will be trained not to duplicate the offer of testing to women who have been offered testing by their GPs.

The GP will ask women if the trial manager can contact them to provide information about the research in order for them to decide if they would like to participate. For those willing to be contacted, a researcher will contact women by telephone, in the first instance, to explain the study and seek consent to participate, allowing time for consideration and questions. The information provided about the study will be based on the patient information sheet (see appendix VIII). This leaflet is described in more detail in the section 'Informing women about the risks and benefits of participation in the study' on Page 18 of the protocol. Those wishing to participate will be asked to sign three copies of a consent form (see appendix IX). More detail on this process is given in the section 'Informed consent to participate in the study evaluation' on Page 19 of the protocol. Data from women will be collected in three ways to minimise data loss: by telephone; face to face; and by post. Fathers of babies of women in Group 1 will be asked if a researcher can contact them about the study if they attend with women for this first appointment. Those not attending will be informed via the women, who will be asked to give the babies' fathers information about the study, including a reply-paid postcard indicating their willingness to participate in the study (see appendix X).

All participants will be asked to complete a Time One questionnaire when they consent to participate in the study; a subgroup of 120 participants will be asked to complete a Time Two questionnaire at about 20 weeks' gestation and a subgroup of 20 women will be asked to complete interviews at about 20 weeks.

**Participation rate**

As described in this protocol we plan to obtain the main outcome data using anonymised data from participating practices. We do not anticipate an unrepresentative participation rate as records from all eligible women will be included.

A secondary outcome measure is informed choice. A sample size of 232 participants per group, allowing for clustering, is required to detect a 10% difference in rates of informed choice, that is 29 women per practice. In a 6-month period it is estimated that 50–75 pregnant women are seen in each practice. In a recently completed cluster randomised controlled trial of the method of conducting antenatal Down syndrome screening, we approached 1292 women: 1156 (89%) agreed to take part and 982 (79%) completed questionnaires.[42] This study took place in a health action zone, i.e. an area with high levels of social deprivation. Thus there are data to suggest that we are likely to obtain an adequate and representative response rate for the secondary outcome measure.

**Pilot study**

We propose to run a pilot study at a general practice in Newham and Lambeth PCTs, prior to data collection, to finalise the protocol without influencing health professionals' behaviour in the study sites.

**Proposed analysis**

We shall compare the relative odds of a woman achieving three outcomes (uptake of screening; uptake of screening by 10 weeks; and the making of an informed choice) for two patterns of care (Groups 2 and 3), and the relative odds of women knowing their baby's father's carrier status as well as their own by 11 weeks (Groups 1 and 2). We shall adjust for confounding variables such as age, parity, ethnicity, education and other indices of socioeconomic status. We will use regression methods for clustered data to estimate odds ratios and their confidence intervals after adjusting for confounders and clustering by care provider. Initially, we propose to use the method of generalised estimating equations. However, since regression methods for clustered binary data can sometimes be associated with problems of non-convergence or biased estimates, we will also investigate whether conclusions are sensitive to the method of analysis by comparing these analyses with results obtained using random effects logistic

regression, or ordinary logistic regression with robust variance estimates.[51] Where anonymised baseline data are available, these will be collected for 6 months in each practice prior to practices receiving training in the new screening protocol. Where retrospective anonymised baseline data are not available, protocols for collecting them will be instigated as practices are recruited to the study, and baseline data collection will take place in the training period prior to recruitment of women. Comparison of baseline data across practices will allow us to evaluate the degree of imbalance in screening outcomes that may have resulted from randomisation of a small number of practices. We will adjust analyses for baseline observations using analysis of covariance as described by Ukoumunne and Thompson.[52] The cluster-specific proportions at baseline will be used for adjustment, as different pregnancies will be evaluated in the two study periods. Secondary analyses will be performed to explore demographic predictors of uptake (including ethnicity, socioeconomic status and age) in relation to the models of care. Rates of informed choice and emotional responses to screening will also be compared across the three study groups.

**Quality assurance and quality control**

Fidelity with the clinical protocol in which training was given, *i.e.* the universal offer of screening, will be assessed by comparing two sets of numbers, that should tally: (1) GP computer records for a 2-week period for the numbers of pregnant women recorded as having been offered screening when the pregnancy is first reported and (2) practice records of the number of women reporting pregnancies during the same period of time. Fidelity with the study protocol will be assessed by comparing the number of patient information sheets given out with the GP and practice records during the same period of time. Any discrepancies will be discussed with the participating practices and efforts made to reduce these.

### *Objective II*

To model the cost-effectiveness of the different patterns of care, using the data generated as part of achieving Objective I.

**Data for the cost-effectiveness study**

If the use of early testing in primary care is shown to be associated with improvements in the screening process (e.g. increases in the proportion of pregnant women undergoing screening by 10 weeks' gestation) compared with those offered screening in community-based secondary care then it is likely that there will be cost implications for both the health-care sector and for the screened women. For example, given that there is a relatively high rate of miscarriage in pregnancies in the first trimester, some women who will undergo early testing in the primary care arm of the trial would not have been tested if the testing were delayed until the booking because a miscarriage is experienced. In addition, parallel testing of fathers in primary care compared with the sequential testing of fathers, if accepted, will have cost implications. Again this is because of the increased risk of miscarriage in the first trimester and because the father is being tested before the results of the woman's test is known, and it is likely that the woman may not be a carrier. Therefore, the economic evaluation will take a broad perspective and consider costs falling both on the NHS and on patients.

As part of the empirical work, key resource use data will be collected to estimate the short-term costs associated with the alternative approaches to screening and diagnosis of women and their baby's father. We will prospectively collect data on training costs and patient-specific resource use. These will include short-term events, such as screening offer, counselling carrier women, fathers and couples, diagnostic testing, and subsequent procedures (e.g. termination of pregnancy) and counselling.

During the semistructured face-to-face interviews with GPs and midwives, information will be collected on their estimates of additional time, both for consultations and administration. These data will be calibrated with data collected in a simple time-and-motion study carried out on a sample of both the primary care practices and the community-based secondary care services. In particular, data on length of consultation time will be recorded for pregnant women who are offered testing as part of a GP consultation, and those offered testing in secondary care as part of a midwifery booking appointment. The additional administrative time devoted to clerical activities as a result of screening in these two contexts will also be collected.

In addition, data on additional resource use and costs, if any, in the laboratory, as a result of the screening, will be collected as part of the study. The unit costs associated with these tests will be accessed from laboratory pricing schedules. Information on other unit costs or prices will then be required to attach to each resource item in order that an overall cost per patient can be calculated. Such data will be collected from relevant routine

sources, (e.g. Personal Social Services Research Unit[53]) and hospital finance departments.

In the acceptability component of the study, a sample of women and their partners will be asked to complete a patient cost questionnaire, which will record the private costs to patients of undergoing screening (e.g. travel costs, time off work, lost income and child-care costs).

**Extrapolating beyond observed outcomes**

The empirical work, described above, will indicate whether the screening alternatives being compared in the trial are associated with differences in three key outcomes: the proportion of women undergoing screening by 10 weeks' gestation; the proportion of women who undergo screening whose baby's father's carrier status is known by 11 weeks; and the proportion of women making informed choices about screening. The main purpose of the modelling component of this project is to allow for extrapolation beyond these observed outcomes, *i.e*. the use of a modelling framework provides the opportunity to predict longer-term antenatal screening outcomes based on the study results of testing. Such longer-term outcomes include: the proportion of all affected fetuses detected prenatally, the proportion of live births, the proportion of terminations of affected pregnancies, the proportion of miscarriages induced by prenatal diagnostic testing, full screening costs and costs associated with long-term rare events.

As a starting point we will make use of two existing models: the simulation model reported by Zeuner *et al.*[7] (programmed in SAS), and the further development of that model, which has been undertaken by Jon Karnon in his work for the National Screening Committee (programmed in EXCEL). [Note that Tony Ades, a coapplicant on this bid, constructed the original model, and Jon Karnon is a member of the research team.] In both models the screening process pathways were depicted for antenatal populations described by ethnic composition, interethnic unions, the frequency of six significant haemoglobinopathy carrier states and the non-carrier state, and the mendelian recessive inheritance patterns. This information allows calculation of the number of homozygous, heterozygous and unaffected fetuses, with their corresponding genotypes, expected each year for any given ethnic composition in the antenatal population. The second function of the model is to put each of these subgroups of an antenatal population through an antenatal and neonatal screening process. Flow diagrams are used to describe the chronological sequence of steps during the screening process.

This research project will develop these models further and use them as a framework in order to allow data from the new empirical work to be incorporated. The trial will produce data on key variables within the cost-effectiveness model, which will inform probability distributions for these parameters. For other model parameters, for which trial data cannot be used to inform probability distributions, these will be described using published data where available.

The new analyses will explore the incremental cost and effectiveness of the alternative screening approaches. The alternative screening policies can be compared in terms of a number of possible incremental cost-effectiveness ratios (ICERs). The most straightforward is the additional costs incurred per additional unwanted affected live birth prevented ('affected live birth prevented' ICER). However, the Zeuner *et al*. model[7] divides mothers with affected fetuses into two groups: those to whom reproductive choice was offered ('choice offered') and those to whom choice was denied ('choice not offered'). This allows alternative policies to be compared in terms of an ICER expressed as the additional costs incurred per additional choice offered ('choice' ICER). This can be extended, using data from this trial, to explore the additional costs incurred per additional informed choice offered ('informed choice' ICER), where choices regarding screening are classified as 'informed' if they are based on good knowledge and if they are in line with a woman's values. In keeping with the guiding principles of the NHS SC&T Screening Programme, the latter is our preferred ICER in this research.

The results of these economic analyses will also be presented using cost-effectiveness acceptability curves to reflect sampling variation and uncertainties in the appropriate threshold cost-effectiveness value. We shall also use both simple and probabilistic sensitivity analyses to explore the robustness of these results to plausible variations in key assumptions and variations in the analytical methods used, and to consider the broader issue of the generalisability of the results. For example, if the screening approaches explored in this research appear cost-effective on the basis of the data collected and analyses undertaken as part of this study, we shall explore the feasibility, costs and cost-

effectiveness of their use routinely in other centres and other settings. This will allow the model to be run to explore not only the cost-effectiveness of universal in high prevalence areas, but also in medium- and low-prevalence areas.

**Using qualitative data and the modelling framework to explore additional policy questions**

The qualitative data to be collected as part of the overall project will identify further possible changes in the organisation and delivery aspects of the screening programmes. Clearly, it will not be possible to explore empirically these additional issues within this research project. However, we will make use of the model framework to predict the longer-term impact of such further policy changes and their overall cost-effectiveness. The level of uncertainty in these further analyses will, by definition, be greater. Uncertainties will be explored using a similar approach to that described above.

### *Research process and management*

**Ethical arrangements for the conduct of studies to achieve project objectives**

The proposed research will be conducted in accord with the Research Governance Framework, involving COREC and research governance approvals.

***Informing women about the risks and benefits of participation in the study***

Potential participants will be informed about the risks and benefits of study participation, in writing and face-to-face, using materials that have been piloted for their comprehensibility and approved by the relevant ethics committees. For women who do not speak English the study will be discussed in a language of their choice using research staff, interpreters or the services of 'Language Line', a telephone translating service. We are working with the London IDEAS Genetics Knowledge Park to develop the materials in languages appropriate to the study populations. A copy of the information sheet is shown in appendix VIII. It follows COREC guidelines on patient information sheets. The written information first outlines the evidence regarding the current failure to offer these tests sufficiently early in pregnancy to allow full reproductive options. Second, it outlines the aim of the study. Third, it indicates that participating in the study may not benefit individual women but should benefit women in the future, and, fourth, that participation will require the research team to examine specific aspects of their records, namely uptake and time of testing. The written information also includes who is being invited to take part, what taking part involves, how the study is funded, the name and telephone number of the trial manager. This information emphasises that participants are free to withdraw at any time and without obligation. Information provided verbally about the study will be based on this written information. As well as COREC guidelines, development of study materials has been guided by MRC guidelines for good clinical practice,[54] liaison with our consumer representatives, services users and the research team. In addition we have worked with the NHS SC&T Screening Programme to ensure that the materials informing women about the study and the screening programme reflect information provided by the National Programme.

***Informed consent to participate in the study evaluation***

In keeping with the practice of cluster trials in which the health-care organisation is the unit of randomisation, consent to receive the pattern of care provided will not be sought. Consent will be sought for women to participate in the evaluation of this care. Women will be asked by the HCP offering screening if a researcher can contact them to inform them about the study and invite them to participate in the qualitative and quantitative evaluation. A researcher will only approach women who agree to be contacted. Written and verbal information about the study in appropriate languages will be provided before consent is sought. After time for consideration and questions, women wishing to participate will be asked to sign three consent forms: one to be retained by the participant, one to be kept in the woman's medical records and one by the researcher (see appendix IX). This discussion will take place in a language and format that is easily accessible to the woman. The research team has considerable experience of negotiating and gaining consent from minority ethnic populations and understands the importance of offering choice in terms of the linguistic and cultural background of the interviewer.

In keeping with MRC guidelines, consent to participate in the research evaluation will not be sought from women aged under 18. Women who do not speak or read English will be informed about the study using an interpreter with appropriate study materials. The trial documentation will be stored for 5 years following completion of the trial. Data will be stored in accordance with MRC guidelines.

**Independent supervision of trials**

The study will be supervised by two committees that are independent of the research team and King's College London, as outlined in the MRC guidelines.[54]

***Trial Steering Committee***

Nola Ishmael OBE, recently retired, as a Nursing Officer in the Department of Health, chairs this committee. Three other people, who are independent of the research team and King's College London, are committee members: Dr Allison Streetly, National Co-ordinator of the NHS SC&T Screening Programme; Ms Audrey Braithwaite Kelly, a service user; and Dr Alison Hill, Department Health Advisor on Genetics. The remit of the committee is overall supervision of the trial. In particular, it will monitor progress against the milestones set in the study protocol, adherence to the protocol as assessed by the quality assurance and quality control measures set out in the protocol, and consideration of new information and safety of participants in the study. It is anticipated that this committee will meet twice a year during the study lifetime. Theresa Marteau, as principal investigator, will attend these meetings and a representative of the funding body, HTA, will also be invited to attend.

***Data Monitoring and Ethics Committee***

This will be chaired by Professor Mahesh ('Max') Parmar, Professor of Medical Statistics and Epidemiology and Head of the Cancer Division of the MRC Clinical Trials Unit. Dr Simon Griffin, Department of Primary Care, University of Cambridge, and Dr Lyn Chitty, Institute of Child Health, University of London, are members of the committee. The Data Monitoring and Ethics Committee will be independent of the research team, Trial Steering Committee, HTA and King's College London, and reports to the Trial Steering Committee. The remit is to monitor study data and make recommendations about stopping the trial. Meetings of this committee are called and organised by Theresa Marteau, principal investigator, but she will attend meetings only if specifically asked to do so by the Chair.

***Study management***

Theresa Marteau and the trial manager Elizabeth Dormandy will review the study on a weekly basis. ED will liaise with research assistants on a daily basis. These reviews will form the basis of monthly research team discussions and two monthly reports submitted to the Trial Steering Committee. A core group of the research team will meet or speak as part of a telephone conference once a month.

**Research team**

Professor Tony Ades, University of Bristol
Professor Elizabeth Anionwu, Thames Valley University
Dr Karl Atkin, University of Leeds
Professor Stirling Bryan, University of Birmingham
Professor Mike Calnan, University of Bristol
Mrs Verna Davis, Manchester PCT
Dr Moira Dick, Lambeth PCT
Dr Elizabeth Dormandy, King's College London
Professor Gene Feder, Bart's and Royal London Hospitals
Dr Martin Gulliford, Kings College London
Dr Hilary Harris, Brooklands Medical Centre
Dr Tracy Johnston, St Mary's Hospital Manchester
Mrs Patricia Jones, University College London Hospitals
Dr Jon Karnon, University of Sheffield
Dr Fred Kavalier, Guy's Hospital
Dr Jane Logan, Mawbey Group Practice
Professor Theresa Marteau (Principal Investigator), King's College London
Ms Tracy Roberts, University of Birmingham
Dr Barbara Wild, King's College Hospital

**Shift research staff**

- King's College London, Department of Psychology:
  - project manager, 3 years, full-time, (Elizabeth Dormandy)
  - research assistant, 2 years, full-time (to be appointed)
  - research assistant, 2 years, part-time (to be appointed)
  - clerical assistant, 2 years, part-time (Hazel Showell)
- King's College London, Department of Public Health:
  - research assistant, 6 months, part-time (to be appointed)
- Birmingham University
  - research assistant, 2 years, part-time (to be appointed).

**Expertise of the research team**

Our research team brings a wealth of local, national and internationally recognised clinical, management and academic expertise, all of which are needed to succeed in conducting a multicentred project in primary- and community-based secondary care, delivering services to a multi-ethnic population. The team brings extensive clinical expertise in primary care, including

providing genetic services to people from ethnic minorities (JL, FK, HH, GF) as well as research on providing genetic services in this context (HH, EA, KA, TM), clinical expertise in SCT (MD, VD), providing laboratory services (BW) and obstetric/maternity care at secondary level (TJ, PJ), training health professionals to provide genetic services (EA, VD), facilitating informed choices in antenatal contexts (EA, KA, ED, TM), and experience in negotiating fieldwork with the various minority ethnic populations that are part of the study population (KA, EA).

Our team also brings considerable relevant methodological expertise in economic modelling (SB, TR, TA, JK), the design and analysis of cluster randomised trials (MG), barriers to HCP implementing change (MC), the measurement of informed choice (ED, TM), and qualitative methods (MC, KA). A further strength of our team is that we can build upon the extensive modelling conducted for the HTA by three of our team (TA, EA, JK), which formed the basis for the universal antenatal screening policy of the NHS SC&T Screening Programme. Our team has close links with the NHS SC&T Screening Programme, with five co-applicants being members of the steering committee for this programme (EA, MD, TJ, JL, TM). Finally, the principal investigator has considerable expertise in successfully delivering large multicentre studies in primary and secondary care.

A small group of consumers have advised and will continue to advise the research team, comprising women and men who have had recent experiences of maternity services, and who are from populations at high and low risk of SCT. They have been recruited through contacts from the SCT centre in Camden, from the Sickle Cell Society and from the National Childbirth Trust. In addition, two workshops will be convened with representatives of the Sickle Cell Society and the UK Thalassaemia Society before the study commences to verify that, within the commissioning brief, we are addressing issues relevant to service users.

**Funding body**
NHS R&D National Coordinating Centre for Health Technology Assessment: £598,569 from October 2004 to September 2007.

## Protocol changes

### *Sample size for Time One questionnaires*

The original protocol stated that we would collect questionnaire data on 100 women per group. This did not include the effect of clustering. Including the effect of clustering indicated that we would require 29 completed questionnaires per group.

***Comment from Martin Gulliford, 8 June 2006 –*** The sample size calculation for the main outcome required 33 women per practice. We achieved a larger sample than this, but, as we did not have sufficient resources to do more questionnaires, we planned to take the first consecutive 33 women who completed questionnaires. This accepted the risk that these might not be fully representative of all women. These 33 per practice will give 90% power to detect a difference in proportion with informed consent between groups of 20% if the ICC for this outcome is about 0.03.

***January 2007 –*** We are unlikely to obtain completed questionnaires on 33 women per practice. Assuming we will obtain 130 completed questionnaires per group we will have sufficient power to detect a difference of between 50% and 70% of women making an informed choice in each group (see email from Martin Gulliford, 12 January 2007, 18.36, stored with team notes 8 February 2007).

### *Place of phlebotomy in practices randomised to Groups One or Two*

*Clarification* – The original protocol stated that 'women wishing to be tested at that time (*first visit in primary care*) will have blood taken either by the GP or practice nurse'. The protocol now states 'Women wishing to be tested at that time will have blood taken using the usual procedure for phlebotomy at the practice', as very few of the practices were able to offer on-site phlebotomy. Details of local phlebotomy practice is given in the care pathway document (stored at j/meetings/health economics/april 6/care pathways paper 3.1).

### *Sample size for women's interviews*

*Sample size for women's interviews* – The submitted proposal stated that120 women would be interviewed and complete Time Two questionnaires. We plan to obtain 120 completed Time Two questionnaires and interview 20 women (see notes of SHIFT team meeting on 30 November 2005).

### *Eligibility of practices*

*Clarification of eligibility criteria for practices* – eligible practices must agree to be randomised to any one of the three groups.

### *Eligibility of women*

The original protocol stated 'Eligible women are those aged 18 and over, wanting to proceed with the pregnancy, and whose carrier status is not documented in primary care records'.

There have been one change and one clarification to the criteria:

***Change –*** Women who confirm their pregnancy in primary care when they are less than 19 weeks 6 days' gestation are eligible (see minutes of DMEC 5 May 2006).

***Clarification –*** All women regardless of age are eligible to be offered the test. Women aged less than 18 are ineligible to take part in the evaluation.

Thus eligibility criteria for women are: '*Women:* Eligible pregnant women attending participating practices who wish to continue with the pregnancy, are less than 19 weeks 6 days' gestation at their first visit to the GP in this pregnancy and there is no written record of sickle cell and thalassaemia carrier status in primary care. All participants offered the test aged 18 or over are eligible to complete the questionnaire'.

### *Data collection period*

***Change –*** Data collection was extended by 1 month to 7 months for the intervention phase (see minutes of DMEC 5 July 2006).

### *Pilot sites*

***Change –***The original protocol stated that 'We propose to run a pilot study at a general practice in Manchester (Robert Derbyshire Practice, Central Manchester) prior to data collection in the two London PCTs to finalise the protocol without influencing health professionals' behaviour in the study sites'.

The protocol was changed to: 'We propose to run a pilot study at a general practice in Newham and Lambeth PCTs prior to data collection to finalise the protocol without influencing health professionals' behaviour in the study sites'. (See research team minutes, 27 January 2005 and 22 November 2005.)

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# Appendix 3

# Towards socially inclusive research: an evaluation of telephone questionnaire administration in a multilingual population

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## Abstract

### Background

Missing data may bias the results of clinical trials and other studies. This study describes the response rate, questionnaire responses and financial costs associated with offering participants from a multilingual population the option to complete questionnaires over the telephone.

### Methods

#### *Design*

Before and after study of two methods of questionnaire completion.

#### *Participants and setting*

Seven hundred and sixty-five pregnant women from 25 general practices in two UK inner city primary care trusts (PCTs) taking part in a cluster randomised controlled trial of offering antenatal sickle cell and thalassaemia screening in primary care. Two hundred and four participants did not speak English. Sixty one women were offered postal questionnaire completion only and 714 women were offered a choice of telephone or postal questionnaire completion.

#### *Outcome measures*

1. Proportion of completed questionnaires.
2. Attitude and knowledge responses obtained from a questionnaire assessing informed choice.

### Results

The response rate from women offered postal completion was 26% compared with 67% for women offered a choice of telephone or postal completion (41% difference, 95% CI diff 30 to 52). For non-English speakers offered a choice of completion methods the response rate was 56% compared with 71% for English speakers (95% CI diff 7 to 23). No difference was found for knowledge by completion method, but telephone completion was associated with more positive attitude classifications than postal completion (87 versus 96%, 95% CI diff 0.006 to 15). Compared with postal administration, the additional costs associated with telephone administration were £3.90 per questionnaire for English speakers and £71.60 per questionnaire for non-English speakers.

## Conclusion

Studies requiring data to be collected by questionnaire may obtain higher response rates from both English and non-English speakers when a choice of telephone or postal administration (and, where necessary, an interpreter) is offered compared to offering postal administration only. This approach will, however, incur additional research costs and uncertainty remains about the equivalence of responses obtained from the two methods.

# Background

Missing data may bias the results of clinical trials and other studies, with low response rates compromising the validity of the findings.[1,2] Acceptable questionnaire response rates are considered to be in the range of 60–70%, with response rates of over 70% described as very good.[3] Self-administered questionnaires sent and returned by post offer a cost-effective way to obtain data from a large number of participants, but often has low response rates. A recent systematic review of methods to increase response rates to questionnaires identified a number of strategies, such as shortening questionnaires, repeat mailing of questionnaires and telephone reminders.[4] Intensive reminders by telephone and post were the most effective, improving response rates by an average of 24%. Financial incentives have also been used to increase response rates.[5] For example a recent descriptive study reported that an unconditional payment of £5 increased the response rate from 78% to 88%.[6]

Some studies comparing telephone and postal response rates from patients have found that response rates from questionnaires administered by telephone are higher,[7] while others have found no difference.[8] Studies comparing responses from general practitioners have also shown varying results. One study reported a lower response rate for postal surveys than for telephone methods,[9] while another found a higher response rate for postal surveys than for telephone methods.[10] Hocking and colleagues suggested that the lower telephone response rate in their study was because practice receptionists blocked telephone access to the general practitioners who were the target of the survey. A consensus is emerging that a combination of direct contact and postal methods leads to higher response rates to questionnaires than the use of postal methods alone.[8,11]

Two areas of uncertainty exist about the use of telephone compared with postal administration of questionnaires. First, research studies not only need a good response rate, but also representative responses from different socioeconomic, demographic and clinical groups. It is not known whether postal and telephone methods of administering questionnaires affect responses differently from different socioeconomic, demographic or clinical groups. Second, responses to questionnaire items administered by post or telephone need to be equivalent. Only two randomised studies have examined this. One found a difference in responses to the same question, while the other did not.[8,12]

The observational study described here took place within SHIFT (Screening for Haemoglobinopathies in the First Trimester), a cluster randomised controlled trial assessing the feasibility, effectiveness and acceptability of offering antenatal sickle cell and thalassaemia (SCT) screening in primary care (ISRCTN00677850).[13] The trial was set in two inner city UK PCTs with a large number of people from minority ethnic groups and with high levels of material and social deprivation. The questionnaires had been designed to assess informed choice about antenatal SCT screening in a population with low levels of literacy.[14]

At the start of the SHIFT Trial, participants were posted questionnaires (in one of 12 languages, selected according to information provided at trial consent) to complete at home and return by post. Initial monitoring indicated that this method gave an unacceptably low response rate. Based on a literature search we developed a second strategy that was more likely to achieve a high response rate in a multilingual population, namely offering participants the opportunity to complete a questionnaire over the telephone with a researcher and an interpreter if necessary. Participants offered the second strategy were also offered postal completion. This paper compares (1) the response rates of offering participants a choice of telephone and postal completion methods with those of offering postal completion only; (2) the responses obtained from the method selected, i.e. postal or telephone completion; and (3) the financial costs to the research team of offering postal and telephone administration of questionnaires in order that reliable estimates can be included in future research cost estimates.

# Methods

## Study design

The study has a 'before' and 'after' design, comparing two methods of questionnaire completion. Eligible participants were asked by their GPs if the research team could contact them to invite them to take part in the trial evaluation and, if so, in which language they would like to be contacted. Women who agreed to be contacted by the research team were contacted in a language identified by the GP as the woman's preferred language, using a telephone interpreter if appropriate, and informed about the trial. For women consenting to take part two methods of questionnaire completion were used:

### *Postal completion only*

A written questionnaire was sent in one of 12 languages and women were asked to return it using a freepost envelope. Up to two reminders to return the completed questionnaire were sent.

### *Choice of telephone or postal completion*

During a telephone conversation to recruit interested women to the trial, women were offered a choice of telephone or postal completion of the questionnaire:

- *Telephone completion* The questionnaire was read to women over the telephone in their preferred language, using a telephone interpreter if necessary. Women were offered the choice of completing the questionnaire at the time consent was sought or at a later stage. A script was developed for telephone administration of the questionnaire, detailing exactly how to present response options. Women who started, but did not finish, the questionnaire over the telephone, were sent a written questionnaire in the post. Up to two reminders to return the written questionnaire were sent.
- *Postal completion* As described above.

## Setting

Twenty five general practices in two UK PCTs. The study represents the first 11 months of the evaluation phase of a cluster randomised controlled trial of offering antenatal SCT screening in primary care.[13] The method of recruiting and retaining representative practices to the trial is described elsewhere.[15] A universal screening policy was operating during the data collection period, that is, antenatal SCT screening was offered to all pregnant women regardless of their ethnicity or family origin.[16] It is estimated that about 6% of pregnant women in the two PCTs carry a significant haemoglobin variant.[16] The two PCTs are ranked among the most deprived in England (sixth and 13th out of 354 boroughs) and have about 40% of their total populations from minority ethnic groups.[17] The questionnaire comprised 32 items, including four items assessing attitudes towards antenatal SCT screening and 10 items assessing knowledge about antenatal SCT screening.[14] It is estimated the questionnaire took participants between 5 and 10 minutes to complete on their own.

## Participants

Seven-hundred and sixty-five pregnant women consenting to take part in a questionnaire evaluation of antenatal sickle cell and thalassaemia screening. The only measure of social group available was 'English speaking' or 'non English speaking'. Women were classified by their GP into these groups, based on whether the woman required an interpreter to speak to a member of the research team. In such cases the GP indicated the woman's preferred language. There were 571 women in the English-speaking group and 204 women in the non-English-speaking group. Sixty one women were asked to complete and return questionnaires using postal completion only. Seven hundred and fourteen women were offered a choice of completing the questionnaire using telephone or postal completion. The uneven group sizes occurred because the response rate from sending questionnaires by post was recognised as unacceptable early in the evaluation phase of the trial and so was discontinued.

## Measures

We report on:

- Response rates for women offered postal completion only, compared with women offered a choice of completion methods.
- Questionnaire responses on two subscales of the questionnaire:
  - Attitudes towards undergoing antenatal SCT screening based on four items. Positive and negative attitudes were defined by the mid-point of the scale, with scores above 12 denoting positive attitudes towards undergoing the test.[18]
  - Knowledge about undergoing antenatal SCT screening based on 10 items. Good and poor knowledge were defined by the

mid-point of the scale, with scores above 5 denoting good levels of knowledge.[14]

- Costs associated with administering postal and telephone questionnaires were estimated by measuring the time taken to (1) administer 50 questionnaires over the telephone and (2) prepare and post 50 questionnaires. Costs were based on the means of these two sets of data. Interpreter costs were estimated from (1) charges made by a commercial interpreting company (£1.50 per minute plus 17.5% tax) and (2) the mean length of time taken to complete 50 interpreted questionnaires over the telephone.

Ethical approval was granted for the study (05/Q0501/36).

## Results

The response rate for women offered postal completion only was 26% compared with 67% for women offered a choice of telephone or postal completion [41% difference, 95% confidence interval of difference (CI diff) 30 to 52] (*Table 1*).[19] Women who spoke English had a higher response rate to a choice of completion methods compared to women who did not speak English (71% versus 56%, 95% CI diff 7 to 23). There were insufficient women who did not speak English and were only sent questionnaires by post to make a valid comparison with women who spoke English and were only sent questionnaires by post, i.e. between English and non-English speakers who were not offered a choice of completion methods.

The preferences and response rates of the subgroup of women offered a choice of completion methods are shown in *Table 2*. Among the women offered a choice of completion methods, 58% chose telephone completion (416/714 95% CI 55 to 62). The response rate for women choosing telephone completion was 98% compared with 23% for women choosing postal completion (75% difference, 95% CI diff 70 to 80). Eight women, having opted for telephone completion, did not complete the questionnaire. Questionnaires were sent in the post to these women. Of these eight, none was completed or returned. Women who did and did not speak English had similarly low response rates to postal questionnaires (23% versus 23%, 95% CI diff –10 to 10). While both groups had very high response rates to telephone completion, women who spoke English had slightly higher rates (99% versus 94%, 95% CI diff 0.7 to 11).

More women were identified as having positive attitudes towards undergoing antenatal SCT screening using telephone questionnaires than using postal questionnaires (96% versus 87%, 95% CI diff 0.006 to 15). There were no differences in the proportion of women identified with good knowledge about the test using telephone or postal questionnaires (31% versus 37% 95% CI diff –6 to 17) (*Figure 1*).

Telephone questionnaires were completed in 20 languages other than English. Postal questionnaires were completed in nine languages other than English.

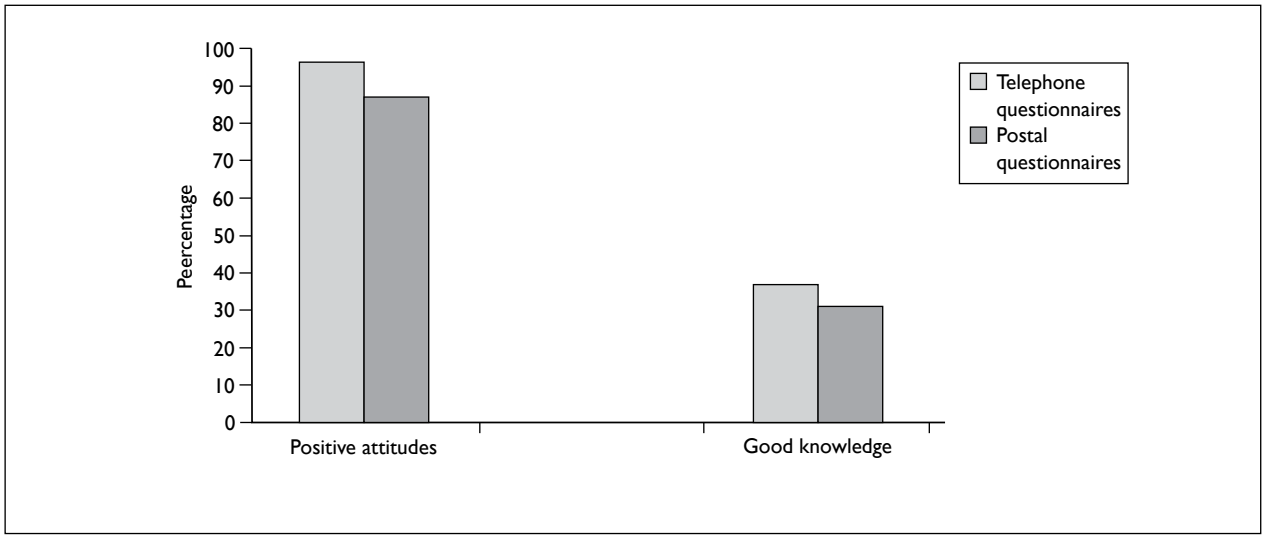


***FIGURE 1*** *Identification of knowledge and attitude from telephone and postal questionnaires.*

***TABLE 1*** *Response rate by questionnaire completion method*

| All women consenting to take part in the trial evaluation (*n* = 775) | Postal completion only (*n* = 61) | Choice of telephone or postal completion (*n* = 714) |
|---|---|---|
| ***Women who do and do not speak English*** | | |
| Questionnaires administered | 61 | 714 |
| Questionnaires received | 16 | 476 |
| Response rate (%, 95% CI) | 26 (16 to 39) | 67 (63 to 70) |
| ***Women who speak English (n = 571)*** | | |
| Questionnaires administered | 55 | 516 |
| Questionnaires received | 15 | 365 |
| Response rate (%, 95% CI) | 27 (16 to 41) | 71 (67 to 75) |
| ***Women who do not speak English (n = 204)*** | | |
| Questionnaires administered | 6 | 198 |
| Questionnaires received | 1 | 111 |
| Response rate (%, 95% CI) | 17 (0.4 to 64) | 56 (49 to 63) |

***TABLE 2*** *Preferences and response rates for women offered a choice of questionnaire completion method*

| All women offered a choice of completion method (*n* = 714) | Women choosing postal response | Women choosing telephone response |
|---|---|---|
| ***Women who do and do not speak English*** | | |
| Questionnaires administered | 298 | 416 |
| Questionnaires received | 68 | 408 |
| Response rate (%, 95% CI) | 23 (18 to 27) | 98 (96 to 99) |
| ***Women who speak English (n = 516)*** | | |
| Questionnaires administered | 193 | 323 |
| Questionnaires received | 44 | 321 |
| Response rate (%, 95% CI) | 23 (17 to 29) | 99 (98 to 100) |
| ***Women who do not speak English (n = 198)*** | | |
| Questionnaires administered | 105 | 93 |
| Questionnaires received | 24 | 87 |
| Response rate (%, 95% CI) | 23 (15 to 32) | 94 (87 to 98) |

## Costs

The costs associated with the administration of questionnaires are:

- *The cost of researcher time to administer telephone questionnaires* The mean length of time to administer the 32-item questionnaire over the telephone was 15 minutes. This equates to £4.50 of researcher time.
- *The cost of interpreters and researcher time to administer telephone questionnaires for non-English speakers* The mean length of time to administer a questionnaire via an interpreter over the telephone was 35 minutes. This equates to approximately £10.60 of researcher time and £61.60 for the interpreting services. Thus, in total it cost £72.20 to administer a 32-item questionnaire over the telephone using an interpreter.
- *The cost of researcher time to prepare and post questionnaires* The mean length of time to prepare and post a questionnaire was 2 minutes. This equates to approximately 60 pence of researcher time.

Compared with administering questionnaires by post, administering a telephone questionnaire cost an additional £3.90 for English speakers and £71.60 for non-English speakers.

## Discussion

The results of this study suggest that offering a choice of telephone or postal completion methods can result in a dramatic increase in response rates compared with postal completion alone. This study was not randomised trial and there could be other explanations for the observed effect. The intervention was complex. It included offering a choice, and offering a choice of two methods that differed in several ways. While we cannot exclude the possibility that the mere offer of a choice was responsible for the effect, the pattern of results suggests that it is the opportunity to complete questionnaires by telephone that is crucial. Telephone completion compared with postal completion allows for ready translation to more languages and provides social support to complete the questionnaire. Perhaps most importantly it removes the reading obstacle to questionnaire completion, thereby allowing the estimated 20–25% of the UK population who are functionally illiterate[20] to participate in the research process.

The increased response rate obtained by administering questionnaires by telephone raises two questions: first, did the increase in response rate vary by social group, and, second, were responses obtained by telephone different to those obtained by post? Regarding differential response rates across social groups, the response from those offered a choice in this study was higher for English speakers than for non-English speakers. The lack of data from non responders means, however, that we are not able to assess how representative the responders are of the telephone or postal groups overall.

The data do not identify a reason why non-English speakers were less likely to opt for completing the questionnaire by telephone than were English speakers. It may reflect a failure of the trial to engage non-English speakers in the research process. Alternatively, it may reflect cultural differences in, for example, willingness to talk to strangers over the telephone. Further work is required to understand why non-English-speaking women were less likely to choose to complete questionnaires by telephone than were English-speaking women. Understanding this may allow telephone administration to be offered in ways that increase acceptability, and hence, use for non-English speakers and thereby increase response rates further.

Comparing responses from the two modalities revealed differences in assessed attitudes: women completing the questionnaire over the telephone were more likely to be classified as having positive attitudes towards undergoing antenatal SCT screening than women completing the postal questionnaire. There were no differences in knowledge by completion modality. One explanation is that the difference may be due to the way the questions were asked or social desirability. Alternatively, it may be because the study was not randomised. That is women who opted to complete the questionnaire over the telephone had more positive attitudes towards undergoing the test than women who completed the questionnaire by post.

There are financial costs involved in offering women a choice of telephone or postal questionnaire completion methods. These include the researcher time to administer the questionnaire over the telephone, as well as the cost of using telephone interpreters. The use of telephone interpreters did not negate the need (or cost) for translating written materials. Research budgets should include funding to cover all these costs.

There are potential problems associated with administering questionnaires over the telephone. The person administering the questionnaire needs to be trained to ensure that the potential participant does not feel under any pressure to participate in the evaluation or to complete the questionnaire. Training is also required to ensure that questions are not asked in a leading way, i.e. in a way likely to guide respondents to answer in a particular way.

For women who opted to complete the questionnaire by telephone, the use of interpreters did not appear to pose any problems. The use of telephone interpreters allows greater flexibility than using written translations because the languages required do not require specifying in advance. However, the use of telephone interpreters does not allow for the use of quality control procedures such as back translation that are available with written translations.

There has been some debate about the use of translation services within the NHS, which cost in the region of £55 million per annum.[21] It has been argued that the use of such services may compound rather than ameliorate the health problems of non-

English speakers by reducing the need for them to learn English and thereby implicitly encouraging non-English speakers to remain outside of the dominant culture.[22] Others have argued that the lack of translation services results in poorer health care for non-English speakers.[23] Whilst this debate is likely to continue within the context of service provision, it is important to acknowledge that this debate is not applicable in research settings. A prerequisite for reliable trials is that trial outcomes are obtained for all participants and are representative of the population in general.[2] They therefore need to include people who do as well as those who do not speak English.

### Strengths and limitations

The strength of this study is that it illustrates the acceptability and feasibility of offering respondents the option of completing questionnaires over the telephone with and without interpreters. A weakness of the study is that the effect of offering telephone administration, although large, is based on observational data, and so uncertainty remains about a causal link between offering women an opportunity to complete questionnaires over the telephone and the observed increase in questionnaire response rates. Whilst the study took place in areas with high levels of social deprivation, individual level markers of social deprivation were not available. It is therefore unknown by how much, if at all, offering telephone administration of the questionnaire increased the percentage of participants with high levels of material and social deprivation. The results also raise questions about the equivalence of responses to questions obtained using the two methods. More research is needed to determine if this is due to differences in types of people responding or differences in demand characteristics of the two methods.

## Conclusion

Studies requiring data to be collected by questionnaire may obtain higher response rates from both English and non-English speakers when a choice of telephone or postal administration and, where necessary, an interpreter, is offered compared with offering postal administration only. This approach will, however, incur additional research costs and uncertainty remains about the equivalence of responses obtained in the two methods.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

ED participated in the design of the study and performed the statistical analysis and drafted the manuscript; KB participated in the design of the study and conducted the telephone interviews; ER participated in the design of the study and helped with drafting the manuscript; TMM conceived of the study, participated in its design and co-ordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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# Appendix 4

## Parameters to inform model

***TABLE 32*** *Haemoglobinopathy carrier frequency by ethnic group*

| | Percentage haemoglobinopathy carrier | | | | | |
|---|---|---|---|---|---|---|
| | Sickle cell carrier (%) | | | | Thalassaemia carrier (%) | |
| **Ethnic group** | **S** | **C** | **D** | **E** | $\beta^{thal}$ | $\alpha^{0\ thal}$ |
| Black Caribbean | 11.00 | 4.00 | 0.05 | 0.05 | 0.90 | – |
| Black African | 20.00 | 3.00 | – | – | 0.90 | – |
| Black other | 11.00 | 4.00 | 0.05 | – | 0.90 | – |
| Indian | 1.00 | – | 1.50 | 0.05 | 3.50 | – |
| Pakistani (female) | 0.05 | 0.05 | 0.05 | 0.05 | 4.50 | – |
| Pakistani (male) | 0.05 | 0.05 | 0.05 | 0.05 | 13.50 | – |
| Bangladeshi | – | – | 0.05 | 4.00 | 3.00 | – |
| Chinese | – | – | 0.05 | – | 3.00 | 5.00 |
| Other Asian | – | – | 0.05 | 0.05 | 3.00 | 1.00 |
| Other | 5.00 | – | 0.05 | – | 1.00 | – |
| Cypriot | 0.75 | – | – | – | 16.00 | 2.00 |
| Italian | 0.05 | – | 0.05 | – | 4.00 | – |
| North European | 0.05 | – | 0.05 | – | 0.10 | – |

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***TABLE 33*** *Probability of a woman booking after 26 weeks' gestation by ethnic group*

| Ethnic group | Probability of a woman booking after 26 weeks' gestation (woman too late for screening) |
|---|---|
| Black Caribbean | 0.046 |
| Black African | 0.081 |
| Black other | 0.041 |
| Indian | 0.078 |
| Pakistani | 0.078 |
| Bangladeshi | 0.078 |
| Chinese | 0.070 |
| Other Asian | 0.078 |
| Other | 0.061 |
| Cypriot | 0.056 |
| Italian | 0.056 |
| North European | 0.041 |

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***TABLE 34*** *Prenatal diagnosis uptake by ethnic group*

| Ethnic group | Probability that woman accepts PND |
|---|---|
| Black Caribbean | 0.13 |
| Black African | 0.15 |
| Black other | 0.13 |
| Indian | 0.37 |
| Pakistani | 0.24 |
| Bangladeshi | 0.19 |
| Chinese | 0.98 |
| Other Asian | 0.50 |
| Other | 0.50 |
| Cypriot | 0.98 |
| Italian | 0.98 |
| North European | 0.98 |

**Note:** When the partner test result is unavailable, the probability that a woman accepts PND is 0.003 times the values in the table. The model allows these probabilities to vary by gestation age, with higher probabilities at earlier gestational ages for some ethnic groups.
**Sources cited by Zeuner *et al.* (1999):** Model B, Anionwu EN. Guidelines for screening for haemoglobin disorders: service specifications for low- and high-prevalence district health authorities. In *Ethnicity and health: review of literature and guidance for purchasers in the areas of cardiovascular disease, mental health and haemoglobinopathies*. York: NHS Centres for Reviews and Dissemination, University of York; 1996. pp. 127–224. Old J. The UK prenatal diagnosis register for haemaglobinopathies (unpublished).

# Appendix 5

## UK National Screening Committee: criteria for appraising the viability, effectiveness and appropriateness of a screening programme

Ideally, all of the following criteria should be met before screening for a condition is initiated.

### The condition

1. The condition should be an important health problem.
2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.
3. All of the cost-effective primary prevention interventions should have been implemented as far as practicable.
4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

### The test

5. There should be a simple, safe, precise and validated screening test.
6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.
7. The test should be acceptable to the population.
8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.
9. If the test is for mutations, the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.

### The treatment

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.
11. There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.
12. Clinical management of the condition and patient outcomes should be optimised in all health-care providers prior to participation in a screening programme.

### The screening programme

13. There should be evidence from high-quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an 'informed choice' (e.g. Down syndrome, cystic fibrosis carrier screening) there must be evidence from high-quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.
14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public.
15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).
16. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money).
17. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.

18. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.
19. All other options for managing the condition should have been considered (e.g. improving treatment, providing other services) to ensure that no more cost-effective intervention could be introduced or current interventions increased within the resources available.
20. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.
21. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.
22. If screening is for a mutation the programme should be acceptable to people who are identified as carriers and to other family members.

## Further reading

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## Feedback

The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

***We look forward to hearing from you.***

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