

## 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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### *Executive summary*

*Health Technology Assessment* 2010; Vol. 14: No. 20  
DOI: 10.3310/hta14200

Health Technology Assessment  
NIHR HTA programme  
[www.hta.ac.uk](http://www.hta.ac.uk)





## 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.

### **Publication**

Dormandy E, Bryan S, Gulliford MC, Roberts TE, Ades AE, Calnan M, *et al.* 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. *Health Technol Assess* 2010;**14**(20).

# NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needed in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

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ISSN 1366-5278

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Published by Prepress Projects Ltd, Perth, Scotland ([www.prepress-projects.co.uk](http://www.prepress-projects.co.uk)), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by Henry Ling Ltd, The Dorset Press, Dorchester.