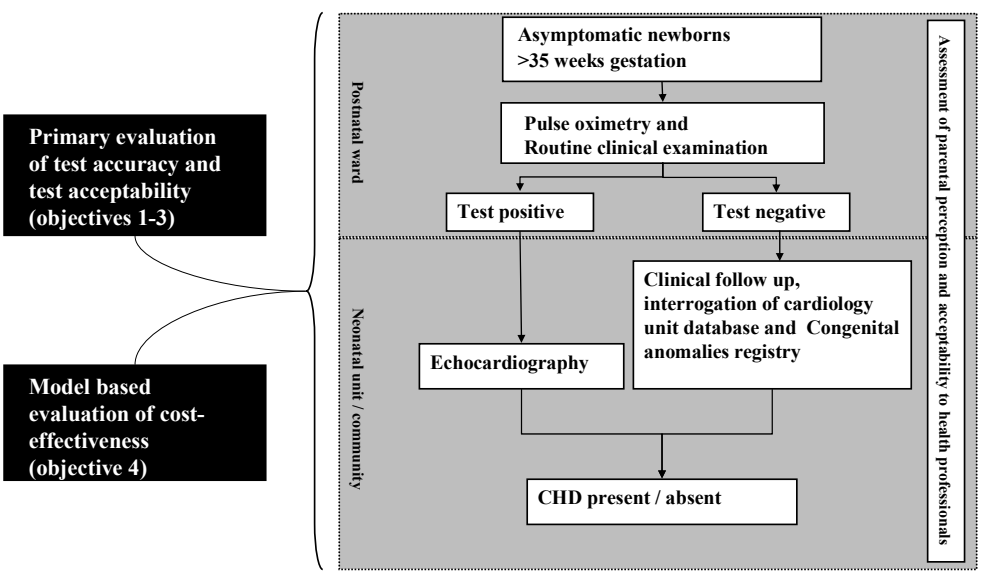
Pulse oximetry as a screening test for congenital heart disease in newborn babies.

PROTOCOL

The Pulse Ox Study aims:

- To develop pulse oximetry (PO) as a feasible screening tool for congenital heart disease (CHD) in newborn babies.
- To determine the accuracy (sensitivity, specificity, predictive values, and likelihood ratios) of PO for diagnosing critical and serious CHD in newborn, using echocardiography / clinical follow up / congenital malformation registries' data as reference standards.
- To determine the psychosocial effect of PO as a screening method among parents and acceptability to health professionals.
- To compare the cost and cost effectiveness of PO and other screening tests (routine neonatal clinical examination and antenatal screening) for improving outcomes of CHD in the newborn using model based economic evaluation.



All women booking into six large obstetric units, in the West Midlands area, will be invited to participate. The study aims to recruit 20,000 women over 12 months for the assessment of test accuracy and acceptability. The main analysis for diagnostic accuracy will estimate sensitivity, specificity, predictive values, likelihood ratios and their confidence intervals. Using multivariable logistic regression analysis, predictive probabilities for various combinations of history, antenatal tests and oximetry results will be generated.

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Protocol Versions

1.0 Submitted to MREC

- 1.1 Incorporates MREC comments
- 1.2 Amendment number 1 – Minor - Administrative changes
- 1.3 Amendment number 2 – Minor - Administrative changes

2.0 Amendment Number 3 – Substantial – Change of eligibility criteria to include babies with extracardiac manifestations of CHD; submission of acceptability questionnaire; submission of Participant Information Booking Flyer, GP Poster and Participant Information Video; minor administrative changes.

3.0 Amendment Number 4 – Substantial – Clarification on data collection and administration of the acceptability questionnaires; clarification on consent procedure; definitions of critical and serious CHD

4.0 Amendment Number 5 – Substantial – Clarification and changes to the methods and analysis of acceptability to health professionals

- 4.1 Incorporates MREC comments with inclusion of staff information sheets. In addition, version number correction of previously submitted staff acceptability questionnaire

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Sponsor

The University of Birmingham is the sponsor. Dr A K Ewer, Consultant Neonatologist, Birmingham Women's Hospital, is the Chief Investigator.

The University of Birmingham is responsible for obtaining necessary approvals and for safety monitoring, the Study Management Committee is jointly responsible for overseeing good clinical practice and the Investigators are responsible for obtaining informed consent and care of the participants.

CONTENTS

1. BACKGROUND

1.1. Clinical Context

CHD is the commonest group of congenital malformations and affects 7-8/1000 live born newborns (1;2). It contributes to 3% of all infant mortality and 46% of deaths from congenital malformations with most deaths occurring in the first year of life. A significant proportion of these children require surgery in the first year. Survival rates for infants with CHD have increased dramatically in recent years and over 80% of children born with CHD will survive to the age of 16 years; this is due largely to improvements in surgical techniques (3). Although the commonest types of CHD do not usually develop serious problems in the neonatal period, there are a number of important cardiac defects which, if undiagnosed, can present with potentially life-threatening cardiovascular collapse in the first few days of life. Although individually less common, when taken together, these lesions contribute significantly to death in infancy. As death or poorer outcome following surgery is much more likely if cardiovascular collapse occurs prior to diagnosis, timely recognition of these cardiac defects prior to collapse is vital in order to improve outcome.

Currently in the UK, all newborn babies undergo a routine screening examination, usually in the first 24 hours after birth, during which, among other things, a careful assessment of the cardiovascular system is undertaken. However, it is estimated that over 50% of babies with undiagnosed CHD failed to be picked up by routine neonatal examination. In addition, some hospitals are deferring this examination and it is then performed by the GP – sometimes up to 10 days after birth. This increases the risk of a baby with CHD presenting with acute deterioration before the screening exam has taken place. Antenatal screening for CHD in high risk pregnancies by fetal echocardiography has been developed and in experienced hands appears a useful technique (4), however a recent HTA assessment review of *routine* ultrasound screening in pregnancy concluded that detection rates for CHD were low (5). The need for an accurate, simple, non-invasive test for CHD in the early neonatal period has led a number of investigators to examine the use of PO and although results are encouraging, as we demonstrated in our systematic review (see below), there is a clear need for a larger, robust, well conducted study to confirm the value, acceptability and cost effectiveness of such a screening programme.

This large multi-centre study will determine the accuracy of PO screening for diagnosing critical and serious CHD in newborns. It will evaluate the acceptability of PO to both parents and health professionals. The study will also assess the costs and cost effectiveness of utilising such screening in combination with clinical examination in the early detection of potentially life-threatening CHD.

1.2. Literature review

1.2.1 Accuracy of PO as a screening test for CHD in newborns

The NHS Research and Development Health Technology Assessment Programme (HTA) commissioned a systematic review of screening for CHD in newborns which was published in 2005 (6). This report included 4 studies examining the role of PO as a screen for CHD in newborns. In 2007, we published a further systematic review of this screening test (7). An extensive search (from database inception to 2006) to retrieve primary and review articles was performed and from a total of 233 citations, 8 relevant studies - 4 more than those included in the previous HTA report (6) - were identified (Table 1). A careful and detailed analysis of the findings were summarised by meta-analysis using the bivariate model, which allows for some variation in threshold. The review can be summarised as follows:

- The quality of the studies was varied in both design and conduct: six studies recruited newborns consecutively (8-13); two were case control studies (14;15) - a

design that biases the results by overestimating the diagnostic odds ratio; two were not prospective (14;15); three studies raise concerns about spectrum bias due to exclusions of antenatally diagnosed cases (10;11;13); none calculated power *a priori*; and sample size was often inadequate to precisely estimate sensitivity.

- There were various thresholds for abnormality of test results (Table 1).
- Only one study explored the added value of PO above the accuracy achieved through clinical examination. The combination of PO and clinical examination had a sensitivity of 76.9% (95% CI, 46.2% to 95%) and specificity of 99.9% (95% CI, 99.8% to 100%) (8).
- None of the studies evaluated acceptability of testing to parents and the psychosocial impact of false positive results or identification of non critical CHD.
- None of the primary studies provided information on cost and cost effectiveness.

Table 1 The accuracy of PO for diagnosing CHD in asymptomatic newborns

Test	*No. of patients*	*Sensitivity % (95% CI)*	*Specificity % (95% CI)*	*False Positive Rate% (95% CI)*	*Timing of the test after birth*
Most commonly used threshold					
saturation* ≤95% foot	11281	60 (14.7-94.7)	100 (100-100)	0	After 24 hrs or discharge
saturation* ≤95% foot or hand	2114	66.7(9.4-99.2)	99.9(99.7-100)	0.1(0-0.3)	As close to discharge as possible
saturation* ≤ 95% foot	3262	96.8(73.6-100)	99.7(99.5-99.9)	0.3(0.1-0.5)	Between 6 and 12 hours
saturation§ <95% foot	5626	25(12.7-41.2)	99.6(99.4-99.7)	0.4(0.3-0.6)	Between 2 hrs and discharge
saturation* ≤ 95% foot	5292	66.7(9.4-99.2)	100(99.9-100)	0(0-0.1)	>24 hrs
saturation§ <95% hand or foot	5211	30.8(9.1-61.4)	100(99.9-100)	0(0-0.1)	Prior to discharge
saturation* <95% foot	2733	75(57.8-87.9)	87.9(86.6-89.1)	12.1(10.9-13.4)	<6 hours of life, at 24hrs of life and/or at discharge
saturation* <95% foot	266	89.4(79.4-95.6)	99(96.4-99.9)	1(0.1-3.6)	12 hours (controls) or prior to surgery (cases)
Most accurate threshold					
saturation* <95% in both limbs or a differential of >3%	266	98.5(91.8-100)	96(92.3-98.2)	4(1.7- 7.7)	12 hours (controls) or prior to surgery (cases)
Summary estimate	**35785**	**63.4(38.7-82.5)**	**99.8(99-100)**	**0.2(0-1)**	summary using bivariate method of meta analysis

* functional oxygen saturation § fractional oxygen saturation

The highest sensitivity seemed to be obtained with a cut off level of functional saturation <95% in both limbs or a differential of >3% in saturation between foot and right hand (15). The false positive rate could be influenced by the age of screening. Performance of the test after 24 hours of birth seems to have the highest specificity (100%) with the lowest false positive rates (10;11). These findings need further evaluation; there are potential concerns that some babies with CHD may present with clinical deterioration before 24 hours and therefore be missed by later screening. There is a clear need for an appropriately designed large test accuracy study evaluating PO as a screening tool for CHD in newborns.

1.2.2 Evidence on effectiveness of early intervention for congenital heart anomalies

In recent years, there has been a significant increase in survival of children with CHD. Developments in ultrasonography have resulted in more precise diagnosis without the

need for invasive procedures, and advances in surgical techniques mean that cardiac conditions which were considered lethal (e.g. hypoplastic left heart) are now routinely offered surgery. However, some cardiac lesions present with acute cardiovascular collapse or death prior to diagnosis. It is clear that if a baby presents with a clinical deterioration before surgery then this leads to worse outcomes (16). It is this group of babies in particular who would benefit from early detection via an appropriate and timely screening technique. This study will pay particular attention to timeliness of PO testing.

1.2.3 Evidence on cost effectiveness of PO as a screening test for CHD

None of the studies identified in the above systematic review had any cost or cost effectiveness data. The HTA systematic review of Knowles *et al* (6) reported the use of a decision analytic model to estimate the cost-effectiveness of clinical examination either alone, or with PO, or with screening echocardiography. The outcome of interest was timely diagnosis of life-threatening CHD, with clinically significant CHD as a secondary outcome. Data from the Northern Region study (1) were used to estimate prevalence of defects and probabilities of outcomes. Unit cost data was obtained by direct observation of a small number of screening tests, contact with manufacturers and published standard costs of management of CHD cases.

Using this model to estimate cost-effectiveness in a hypothetical population of 100,000 live born infants, it was estimated 82 cases of life-threatening CHD would be identified using a combination of PO and clinical examination, compared with 39 cases by clinical examination alone. The costs of the screening programmes would be £480,000 and £300,000 respectively, or an additional cost of £4,900 per additional timely diagnosis for the combined strategy. The cost of using screening echocardiography alongside clinical examination was prohibitive at £4.5m per additional timely diagnosis with a four-fold higher false positive rate. Although sensitivity analysis showed the findings are robust to many parameters, detection rates and screening tests costs influence cost-effectiveness greatly. The model assumes the screening tests are performed at 24 hours of age, whereas, if this test were to become routine, it would most likely be performed much earlier. The time of diagnosis is a major difference from this study: detection rates influence the model yet no data exists to demonstrate the impact of timing of diagnosis on test performance.

1.3. Objectives of the Pulse Ox Study

The objectives of the study have been framed to assess PO for screening for CHD in newborn babies in a hierarchical fashion, based on methodologically robust frameworks for evaluation of diagnostic tests outlined by Guyatt *et al* (17) and Fryback and Thornbury (18), as follows.

- To develop PO as a feasible screening tool for CHD in newborn babies.
- To determine the accuracy (sensitivity, specificity, predictive values, and likelihood ratios) of PO for diagnosing critical and serious CHD in newborns, using echocardiography / clinical follow up / congenital malformation registries' data as reference standards (see Appendix E for CHD definitions).
- To determine the psychosocial effect of PO as a screening method among parents and acceptability to health professionals.
- To compare the cost and cost effectiveness of PO and other screening tests (routine neonatal clinical examination and antenatal screening) for improving outcomes of CHD in the newborn using model based economic evaluation.

2. STUDY DESIGN

2.1. Brief summary

The current neonatal screening for CHD involves a clinical examination undertaken either by a trained health professional prior to discharge from hospital, or by a GP up to 10 days following delivery. The study will evaluate screening using PO undertaken by a midwife within 24 hours of birth. The primary analysis will be accuracy of PO in detecting life-threatening CHD. A comparison of the performance of PO either against, or in addition to, antenatal screening will be made by multivariable logistic regression analysis; another with postnatal clinical examination will be made by decision analytic modelling. The study will also assess parental perception and acceptability to healthcare staff. A cost-effectiveness analysis comparing different screening strategies will be undertaken, using direct study data where possible, in a model-based economic evaluation.

2.2. Overview

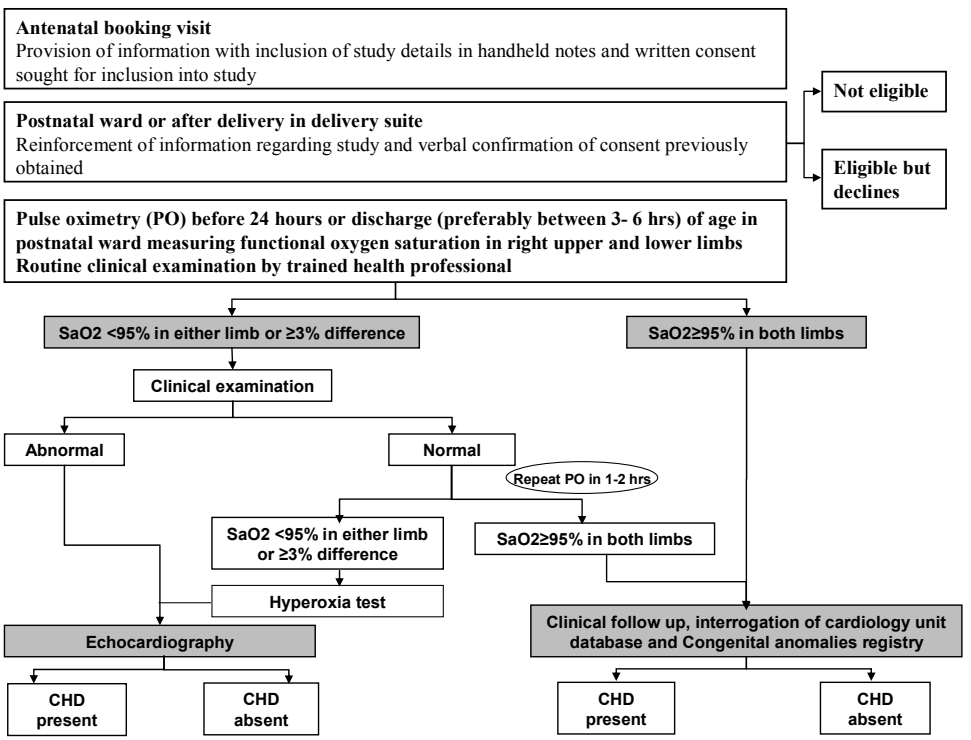

Figure 1: Flow chart of study organisation

This study will assess the accuracy, effectiveness and efficiency of PO in a delayed-type cross-sectional accuracy study. First, PO will be performed soon after delivery in all cases, which will have the advantage of identifying potentially serious low oxygen saturations in a timely fashion before symptoms are apparent. Integrating PO into the assessments performed routinely by the midwife when mother and baby are transferred from the delivery suite to the post-natal ward will make this design practicable and achieve maximum recruitment. Testing will occur early but over a range of times within the first 24 hours after birth (usually within 3-6 hours) or before discharge, allowing analysis of the optimum time for PO screening. After conducting PO, we will use different reference standards for test positive and test negative cases: echocardiography for the former and follow-up for the latter.

In this design, it would be unlikely that the subsequent clinical examination could be performed independently of the PO results, as midwives would want to alert the medical staff to a low saturation. This precludes a direct comparison of PO against clinical examination, as the latter would be prone to work-up bias. This comparison will be made through decision-analytic modelling using unblinded and historical data for input and appropriate sensitivity analyses conducted.

Clearly, in the presence of a feasible and accurate CHD screening strategy, there will be a need to consider the cost-effectiveness. The cost-effectiveness of PO in combination with postnatal clinical examination will be evaluated against examination alone and examination and antenatal screening, in a model-based analysis. Two systematic reviews of the performance of antenatal screening for CHD in first trimester (4) and second trimester (19) have been performed. Data on this group will be collected as part of our study. Using directly obtained information on outcomes and costs from a large number of babies in a real-life setting, the implications of all methods of identification of CHD will be modelled, thereby improving the generalisability of the results.

2.3. Test accuracy study design

A test accuracy study is different to an effectiveness study in that randomisation of subjects is not involved. An outline of the test accuracy study is shown in Figure 2. It is designed to generate a comparison of measurements obtained by index tests with those obtained by reference standards. In this way the accuracy of index tests can be estimated. A reference standard is a test that confirms or refutes the presence or absence of disease beyond reasonable doubt. Therefore it is sometimes also known as the gold standard. PO is the index test whereas the reference standard will be the identification of CHD cases up to one year through echocardiography, databases maintained by the West Midlands congenital anomaly register (CAR), regional cardiology referral unit, regional perinatal mortality survey, hospital information departments and, if necessary, READ codes of primary care trusts.

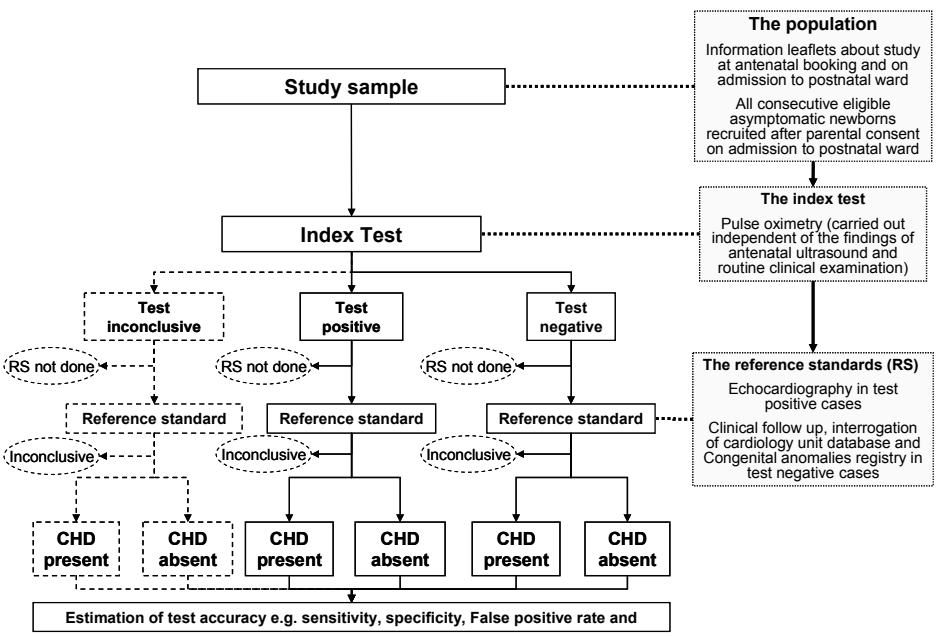

Figure 2 Flowchart of test accuracy study of PO as a screening tool for CHD in newborns

2.4. Large, simple study: minimal extra workload

In order to obtain the large number of patients necessary for the reliable evaluation of the PO test, the study will need the participation of more than one centre. To make these practicable, study procedures need to be kept simple, with the minimal extra workload placed on participating clinicians, beyond that required to manage their patients. This will be achieved by simple entry procedures, early consent of women, the use of standard local testing regimens, minimising documentation and streamlining data collected procedures. Regular newsletters will keep collaborators informed of study progress, and regular meetings will be held to report progress of the study and to address any problems encountered in the conduct of the study.

2.5. Setting

The setting will be 6 large maternity units in the West Midlands region. These units are based in the following hospitals: Birmingham Women's, Heart of England, City (Birmingham), New Cross (Wolverhampton), University Hospital of Coventry & Warwickshire (Coventry), and Royal Shrewsbury. These units serve a large, socio-economically and ethnically diverse population, which will aid generalisability of findings and have a large total number of deliveries (over 30,000 per annum). The units also represent the spectrum of obstetric settings, from a busy district general hospital to a specialised tertiary referral centre.

3. ELIGIBILITY

3.1. Eligibility criteria for the test accuracy study

The following inclusion / exclusion criteria will be used:

3.1.1 Inclusion criteria

Mother	Given written informed consent for screening and follow-up through databases
Baby	Gestational age ≥35 weeks
	Asymptomatic at birth, regardless of antenatal risk factors or ultrasound findings

3.1.2 Exclusion criteria

Mother	Unable to give consent through incapacity, inability to speak English and lack of interpreter
Baby	Symptoms of cardiovascular abnormalities at birth

3.1.3 Inclusion of babies with suspected CHD from antenatal ultrasound

Babies suspected of having CHD, following antenatal ultrasound, will be included in the study. These pregnancies will be managed under the care of a consultant and will be transferred shortly after birth to a neonatal unit, where they will routinely have PO monitoring. The first reading, prior to any therapy or oxygen administration, will be recorded for the purposes of the study (provided the baby is asymptomatic at the time).

The evidence from the review about the accuracy of midtrimester fetal ultrasonography (19) showed that this antenatal test was not without error and it did not lend support to its routine use among unselected and low risk populations. In fact, practice concerning the intensity of such screening across the UK varies considerably, as does associated test performance. The West Midlands region, however, has an active, specialist-based fetal echocardiography screening programme for high-risk mothers, which detects a significant proportion of fetuses with CHD. Most babies born with a positive antenatal test result are

asymptomatic at birth, would comfortably meet all our inclusion criteria (see sections 3.1.1 and 3.1.2), and would have been eligible for mass screening with PO, regardless of antenatal screening, whether risk or ultrasound based. In babies with positive antenatal scan, PO is currently routinely carried out after birth on admission to the neonatal unit, so it would be unwise to disregard this information. There is no risk of introducing bias in PO estimation due to prior the suspicion of CHD as PO is an objective test. By including this subgroup, the overall CHD prevalence will be increased, thereby increasing the power and precision. It will allow the opportunity to explore variation in test accuracy in different population spectra and will help determine the added value of PO over and above what is achieved by antenatal screening. This information will be critical input into the decision-analytic model.

3.2. Recruitment of participants

Although PO will be introduced as a routine post-natal test, consent will still need to be obtained from each mother for the purposes of the study. Ideally consent is sought under unhurried circumstances, when entry criteria are fulfilled. These two issues may not be easily satisfied simultaneously in this study, as the setting involves obtaining PO readings in the first few hours of the baby's life. Consent will be sought in stages:

- A patient information leaflet will be given to all pregnant women at the time the mid-trimester ultrasound scan, or at any time after the scan but before birth, by the community or antenatal clinic midwives. The leaflet will also be made generally available and prominently displayed in various areas within the participating hospitals and their community antenatal clinics. This leaflet will be available in different local languages to reflect the ethnic communities at each centre.
- The leaflet will emphasise that PO is being introduced for routine use in the participating hospitals for the duration of the study, but that parents are entitled to choose whether or not they want their baby screened. Parents will be advised to discuss the study with the community or antenatal clinic midwife if they have any questions; and the phone number of the local coordinating midwife for the study will be provided.
- A coloured sticker confirming that the leaflet has been passed to the mother will be attached to the front of her notes. A copy of the information leaflet and consent form will be included in the hand-held notes. Any parent declining PO before delivery will have this recorded in the maternity notes.
- The consent form can be signed by the mother at any point before delivery and countersigned by the community or antenatal clinic midwife. At the time of testing, the consent will be reconfirmed verbally and any change recorded on the consent form.

Where necessary, appropriate interpreters will be asked to aid discussion relating to study participation. Some of the study centres employ link workers, who cover the role similar to community midwives for non-English speaking mothers. They are ideally suited to taking consent for non-English speaking mothers for this study.

It is anticipated that acceptability of the pulse oximetry test and willingness to participate in the study may potentially vary between ethnic groups. We will record baseline demographic and ethnicity information from all mothers invited to take part, including those who decline to take part, those who miss consent, or those who are later identified as ineligible. We will collect mother's hospital number, age, parity, ethnicity and language. These details will be stored anonymously. This will establish the take-up rate of the study.

By making PO a routine test in each hospital, it will become embedded in the care pathway for women post-delivery, removing the possibility that women are missed by

mistake, apathy or poor organisation. In this study, reasons for opting out will not be collected (unless it becomes apparent that this is an issue), nor will it be necessary to obtain all mothers' addresses. We anticipate a high take-up, making it unfeasible and unnecessary to collate excess information when it will be available from routine hospital data or can be collected postnatally.

All community midwives and link workers will receive training regarding the introduction of PO screening, information about the study and instruction on their roles from the local coordinating midwives. This will occur during community team meetings and the information provided will be reinforced periodically throughout the study by further meetings and newsletters from the Study Office.

3.3. Consent

The conduct of the study will be in accordance with the Medical Research Council (MRC) Guidelines for Good Clinical Practice 1998 and any subsequent amendments. The mother's written informed consent (according to usual local practice) to participate in the study must be obtained before testing. As the study is of short duration and has no consequence on the management of pregnancy or any post-natal care, the women's GP will not be notified of her participation in the study.

3.4. Organisation of Recruitment

Recruitment will be organised and supported by dedicated midwife leads, who will work with local community and antenatal clinics midwifery teams and obstetrics and neonatal leads. We believe that that the following strategy is likely to be successful in achieving maximum recruitment.

- Appointment of a dedicated coordinating midwife at each centre with responsibility for overseeing preliminary consent in the community and at the antenatal clinic of her centre, PO testing on post-natal ward and for data collection and problem resolution.
- Appointment of a lead research midwife at Birmingham Women's Hospital, who will liaise with all the coordinating midwives at each centre and coordinate the screening at this hospital, provide training and trouble-shoot recruitment and midwifery problems.
- Provision of simple written study information (similar to the "Newborn blood-spot screening" leaflet), supported by face to face discussion with midwifery staff in antenatal clinics and the community.
- Regular, close communication with midwifery staff in the community, antenatal clinic and post-natal wards.
- Training of midwifery staff on post-natal ward in obtaining PO readings, as the coordinating midwife will not be available to undertake this task on all babies.
- Provision of regular feedback on progress in study recruitment, including individual hospital teams' performance and progress against targets.
- Regular newsletters to all relevant staff involved in the study.

4. TESTS AND PROCEDURES

4.1. The index test

It is essential to explore the technical and practical aspects of conducting the PO test before the commencement of the accuracy study. A ward-based technical feasibility study will be carried out to establish the most practicable methods of testing and reporting results in the postnatal ward setting. This will also allow the development of programmes

for quality assurance and for training staff to perform PO. This will be one of the roles of the coordinating midwives.

The pulse oximeter used in the study is from the Radical® series from Masimo (Irvine CA, USA). These have been shown to outperform other oximeters in that the recording is free from motion artefact and is capable of achieving stable, accurate readings in an active subject and also when perfusion is low. Five oximeters will be available in each maternity unit in order to ensure readings can be taken at all times and to ensure readings are not missed because of faulty or misplaced machines. An oximeter will be available on both the postnatal ward and delivery suite.

The participating centres have agreed to make it standard practice to perform PO within each unit and the clinical protocols changed accordingly. PO will be performed before 24 hours or discharge, preferably at around 3-6 hours of age which corresponds to admission to the postnatal ward. PO is routinely performed on babies on the Neonatal Unit. It is painless, extremely well tolerated by babies and requires minimal clinical training. It is estimated that to perform saturations on one hand and one foot will take no more than five minutes. The results of the PO will be recorded as percentage functional saturation for each limb. The date and time of testing will also be recorded. A cut off of $<$95% in either limb or a difference of ≥3% between the limb readings will be considered to be abnormal. This threshold has been shown in previous studies to have the highest sensitivity. It also has the potential to detect coarctation of aorta, a treatable condition that has been missed in earlier studies with different thresholds (14,15) It is anticipated that the maximal sensitivity of the test is achieved by about 6-12 hours of age (9;14;15), by which time we anticipate the majority of babies in this study will have been screened. If PO is low and the clinical examination is unremarkable, the PO will be repeated 1-2 hours later for a definitive definition of abnormality. If the saturations remain low, oxygen will be administered (nitrogen washout or hyperoxia test) to identify potential respiratory causes for low saturations. An echocardiogram will be performed in all case of persisting low saturations (i.e. test positive cases)

4.2. Clinical examination

Physical examination of newborns is recommended in the NICE clinical guidelines "Postnatal Care of Women and their Babies section 1.4.11' and should occur within 72 hours of birth. Assessment of the cardiovascular system should include checking the position of the heart, heart rate, rhythm and sounds, murmurs and femoral pulse volume. Each hospital will have a protocol for the timing and content of the postnatal examination and this study will not attempt to alter clinical practice, although the NICE guidelines will be promoted. The assessment is usually performed before discharge from hospital by senior house officers or registrars but may also be performed by senior midwives or advanced nurse practitioners.

Some of the participating units, in certain circumstances, defer the clinical examination, to be performed by the GP up to 10 days after birth. All GPs in the catchment areas for the participating hospitals will be informed of the study through a flyer, together with posters for the waiting room and supplies of the information leaflet. Where GPs may be called upon to perform the clinical examination, further information regarding the study will be provided in the mother's postnatal notes, together with copies of the data collection form and envelopes to return the information to the hospital.

4.3. The reference standard

The reference standard will be a combination of the following approaches.

4.3.1 Echocardiography

Echocardiography is a resource intensive procedure, and will only be undertaken on those with symptoms or signs at clinical examination (as is current practice) or those with low PO readings. Given an assumed performance of 75% sensitivity and 99.5% specificity, and an overall prevalence of 5 per 1000, in our design, we would expect 9 per 1000 to undergo echocardiography based on low saturation by PO or symptoms apparent at clinical examination and between 40-50% of these will have clinically significant CHD. Thus we anticipate between 200 and 300 extra echocardiographic examinations during the study. To enable the participating hospitals to cope with this increased demand, a specially appointed clinical research fellow will be able to visit centres to perform echocardiograms when the hospital cannot accommodate them themselves.

4.3.2 Congenital anomalies registry

At periodic intervals after recruitment, the regional congenital anomalies register (CAR) and mortality register will be queried using the diagnostic codes for cardiac abnormalities. Information retrieved will include the baby date of birth, location, date and nature of the diagnosis, any known outcome, including death and the baby's NHS number We will also collect details on the diagnosis of Down's syndrome or any other congenital anomaly. Other identification details will be stripped to enable data transfer compliant with the Data Protection Acts. This will be sent to the Study Office to be cross-referenced with the babies already on the study database, matching for Baby and Mother NHS numbers and baby date of birth. For those that match, diagnostic information will be transferred to the study database for analysis. Unmatched babies will either have been missed at study hospitals, been born at non-participating hospitals within the region or have been born outside the region. These figures will help inform the study of completeness of verification. Additionally, registry holders in adjacent regions (e.g. Mersey and Trent) will be asked to be vigilant for notification of CHD cases from the West Midlands region.

A similar process will occur at the Birmingham Children's Hospital, which is the tertiary referral centre for the entire region. As the study progresses, if it appears that not all cases are being collected through either of these two methods, regional primary care trusts may be approached to search their databases using diagnostic READ codes. This will be substantially more labour intensive, so methods to maximise identification of CHD through the CAR and Children's Hospital sources will be explored first.

4.4. Compliance and follow-up issues

The issues of compliance and follow-up in diagnostic accuracy studies are of a different nature to those of randomised trials of interventions. In the systematic review of PO as a screening tool, none of the studies reported specific problems about parental non-compliance, i.e. declining participation after having given consent to take part. The key issue for us is the timing of the PO test to avoid loss of participation after consent has been obtained. The study has been designed to tackle this issue by performing the test in the first few hours after birth, on admission to the postnatal ward, which has the added advantage of early detection of life-threatening cardiac disease prior to the onset of symptoms, a situation that can worsen the prognosis. Although it not possible to anticipate how many babies presenting late with CHD will not be captured by the study, it is not anticipated that this will be above 5%, given the measures described in section 4.3. This figure would be estimated from the number of mis-matches arising from the CAR and presented at the interim analysis to provide an opportunity to re-calculate sample size, if required.

4.5. Quality Control

Quality assurance of testing will begin with a clearly documented staff training programme. A register of staff who have been trained, and their competence assessed will be maintained, and only staff whose names appear on this list will be permitted to undertake testing. Staff will also receive regular update training, and periodic reassessment of their competence.

4.6. Serious and unexpected adverse events

There are no foreseeable risks of mortality or significant morbidity associated with testing. Every effort will be made to minimise any risk through training. All **serious adverse events**[*] believed to be associated with the study should be reported by fax to the Study Office as soon as possible. This report should be followed within 2 weeks by a completed SAE form.

4.7. Other management at discretion of local doctors

All other aspects of patient management are entirely at the discretion of the local doctors. Mother and child are managed in whatever way appears best for them, with no special treatments and no extra follow-up visits.

5. OUTCOME MEASURES

5.1. Protection from bias

There are many possible sources of bias in accuracy studies (20) and these have recently been highlighted in the STARD statement (21). Selection bias may arise if the sample is not suitably representative of the population. This is likely to occur with use of non-consecutive or convenience sampling. The study will seek to recruit all consecutive eligible newborns. A related issue is that of spectrum bias whereby the accuracy of tests varies among study samples with differences in disease spectrum i.e. prevalence of CHD. It is possible that centres that perform fetal echocardiography may diagnose more newborns antenatally, thus affecting the spectrum composition. Information on PO testing and clinical examination of symptomatic newborns with suspected CHD will be collected and those newborns that were antenatally diagnosed to have CHD. Sensitivity analysis will explore the variation in test accuracy due to spectrum composition.

The PO testing procedure will be standardised in the first phase of the study and criteria for interpretation and thresholds have been determined *a priori* (7).

The use of different reference standards for test positive and test negative cases is not ideal but this is the most practicable way to verify presence or absence of disease. Empirical studies have shown that studies with differential verification produce more biased estimates of accuracy than studies with complete verification by the preferred reference standard, particularly when differential verification is not pre-specified in the design or completely at random. The direction and magnitude of bias is likely to depend on whether differential verification will lead to different detection rates of CHD under different reference standards. If complete verification by the preferred reference is not possible and different reference standards have to be used, the best approach is to incorporate differential verification in the design (22), the approach used in this study. With this design, the estimates of positive and negative predictive values under the two reference standards, the key parameters for decision analytic modelling, will escape any bias or interpretive problems. The estimates of sensitivity and specificity will also escape any

[*] For the purposes of this study, "**serious**" adverse events are those occurring in either subjects or testers which are fatal, life-threatening, disabling or require some form of medical or surgical treatment.

difficulties in interpretation as the focus will be only on clinically significant CHD which is likely to be detected equally well by both reference standards.

One of the conclusions that arose from the recent systematic review is the need for a large well conducted study, aimed at improving the precision of the sensitivity estimate of the test. The sensitivity of PO as a screening test for CHD varied between 25% (95% CI, 13% to 41%) (12) and 98.5% (95% CI, 91.8% to 100%) (15) in previously conducted studies. The performance of the test, particularly estimates of sensitivity depends on the absolute number of patients with disease. Thus there is imprecision of the sensitivity estimates due to the low prevalence of CHD in relatively small studies. This study has been planned to be large enough to achieve good precision, as shown in section 6.1.

5.2. Primary outcome measures

These will be the accuracy of each index tests for detection of CHD, expressed as sensitivity, specificity, positive and negative predictive values and positive and negative likelihood ratios, together with 95% confidence intervals.

5.3. Secondary outcome measures

5.3.1 Clinical Examination

The presence or absence of irregularities in heart rate, rhythm and sounds or murmurs and suspicion of cyanosis observed through clinical examination will be noted. The date, time and grade of person performing the test will be recorded.

5.3.2 Assessment of patient acceptability

We define acceptability broadly in this study to incorporate the psychological impact of screening on parents. We will examine acceptability of pulse oximetry to parents using a structured questionnaire. The questionnaire will be designed specifically for the study incorporating standardised measures as appropriate. It will be administered as soon as is practicable after testing to limit recall bias whilst being sensitive to the distress of parents. As far as possible, the questionnaires will be administered before mother and baby are discharged. Otherwise, if appropriate, the questionnaire will be sent to the mother by post. Mothers will not be approached until the local clinician/midwife feels it is appropriate and face to face or telephone interviews will be offered as appropriate. Mother's address and telephone number will be collected as necessary.

Parents of all babies who screen positive, i.e. all true positive and false positive cases, will receive the questionnaire or a structured interview based on the questionnaire. All parents of children with CHD who screen negative, i.e. the false negative cases, will also be approached at a later stage. Finally a sample of the largest group will be approached: parents whose babies do not have CHD and who screen negative, i.e. the true negative cases. The inclusion of all four groups of parents will enable the differentiation of the impact of screening *per se* from that of the outcome of screening.

In designing the questionnaire it will be important to maximise the precision and validity of the instrument. As this is not a randomised-controlled trial, no comparison across testing procedures will be carried out where maximum differences in scores would be expected. Therefore the instrument must measure acceptability as accurately as possible so that any differences between sub-groups (e.g. socio-economic, ethnic) can be discerned. In order to maximise face and content validity, preliminary focus group discussions will be held with:

- parents of children with CHD diagnosed postnatally
- experienced midwives and paediatricians
- representatives of paediatric cardiology support groups (e.g. Little Hearts Matter)

From these, a set of items will be derived which will seem relevant to the participants and cover all the areas thought to be important by participants.

Pilot testing will be carried out to make certain the questionnaire is usable. It is anticipated that the questionnaire will measure acceptability and satisfaction in the following areas:

- the procedure(s) for testing
- the information provided when consent is obtained
- processes for giving test results.

Parents will also be asked whether they would be prepared to have PO testing after future births, or recommend it to others, since these give the most reliable measures of satisfaction. In addition, comparisons will be made using all data across social, ethnic, age and parity groups to see if testing is acceptable across all groups and, if it is not, the areas where acceptability is low and negative impact is high, so that procedures may be reviewed.

5.3.2.1. Measuring Distress

Psychological distress will be assessed across the populations using standardised instruments, so that levels of distress can be compared to population norms and to levels measured in other screening studies. Specifically we will use:

- State anxiety form of the Spielberger State-Trait Anxiety Inventory (STAI). This instrument has been widely used and validated in a number of clinical studies on screening (23;24). It is a short, closed format questionnaire of current anxiety levels.
- Depression subscale of the Hospital Anxiety and Depression Scales (HADS). Again this instrument has been widely used and validated in clinical studies as a measure of mood, including previous screening research (23). Some of this literature has been reviewed in a systematic review (25).

In order to understand variations in acceptability and the impact of testing on distress levels, measures will also be taken of possible explanatory variables including:

- Illness perceptions of CHD which will be measured using a brief version of the Revised Illness Perceptions Questionnaire (26).
- General optimism which will be measured using the 2 item short form of the Life Orientation Test (27).

5.3.2.2. Assessment of parents who receive false positive results

The literature on antenatal and neonatal screening suggests that the effects of false positives may extend over considerable periods of time in some circumstances (28-31). In part this may be due to the information and support provided for such parents (32;33). However other work contradicts this and suggests the high levels of anxiety are dispelled by diagnostic tests showing the baby is healthy. Given the contradictions in the literature, parents receiving false positive results will be assessed after testing and at the one year follow up. This will give us an indication of both the degree and duration of distress caused by the outcome. If there is significant change over this period, a second assessment will also give a better indication of the acceptability of PO screening to this group. Given that some of the literature on false positives results suggests an impact on the parent-child bond, a parental bonding questionnaire will be administered at both time points.

5.3.2.3. Assessment of parents who receive false negative results

Parents who have received false negative results will not be definitively identified until the 12 month follow-up stage of the project. So, although some may have been included in

the sample of parents receiving negative results, the main assessment of these parents will occur at that stage and no formal comparison with their immediate post-testing perceptions will be possible within the time-frame and scope of the project.

5.3.2.4. Assessment of acceptability to health professionals

The acceptability of PO as a routine procedure to health professionals will be addressed by holding focus groups with midwives, midwifery assistants and other staff who carry out the test (for example nursery nurses and health care assistants) at Birmingham Women's Hospital and one of the other study centres after they have had experience of this (see Appendix H for information sheet). Issues to be explored will include perceptions of the efficacy of testing, costs to staff in terms of time and effort involved, perceived benefits of testing, professional views on the impact on parents. The discussions of the focus groups will be recorded, transcribed and analysed using inductive thematic analysis.

To address the acceptability of PO to neonatologists, echocardiographers, registrars and senior house officers (SHOs), staff at all study centres will be invited to complete open-ended questionnaires administered by e-mail (see Appendix G for information sheet). Focus groups for these groups would not be feasible because of the rotation of posts for registrars and SHOs. Issues to be explored will be similar to those addressed in the focus groups (see Appendix F for questionnaire; precise wording/details may be amended following further discussion with professionals and piloting). In order to allow participants to respond to the thoughts of their peers, an anonymised summary of responses will be compiled and emailed to participants, with the invitation to add further thoughts. Participants will not be identifiable to each other; all participants will reply to the researcher and not to each other. Responses will be analysed using inductive thematic analysis.

5.4. Additional information sought

In addition to the PO and clinical examination information, a minimal demographic and clinical dataset will be collected (see Appendix D). Some additional data will be collected postnatally. This will include baby birth weight and mother ethnicity. If there was an antenatal diagnosis or suspicion of CHD, limited information on the ultrasound findings will be extracted from the maternity notes. The baby's NHS number will be used as the primary identifier. All babies are issued with unique NHS numbers and these are used to track individuals throughout the NHS, making it a safe identifier. Addresses will not be collected on all mothers for the purposes of the study, to reduce the amount of identifiable data transferred out of the hospital. Addresses and telephone numbers will be collected for only a small sample of mothers for the administration of the acceptability questionnaires (see section 5.3.2)

5.5. Health economic outcomes

5.5.1 Perspective and cost data collection

If PO screening is shown to be an effective adjunct to the standard practice of use of clinical examination to screen for CHD in newborn babies, then it is likely that important cost implications will be seen for the health care sector. For example, PO may detect additional cases of abnormality compared to standard clinical examination alone which increase the number of echocardiograms required and increase the number of cases of infants requiring cardiac surgery (i.e. babies that could have had surgery but died before this was possible). But the additional associated costs of early diagnosis and treatment may lead to a reduction in costs associated with undetected CHD and avoided complications. Given this, the economic evaluation will take the perspective of the NHS.

Resource use data will be collected to estimate the costs associated with the additional use of PO in screening newborn babies. Data on NHS resource use will be prospectively collect for a sub-sample of the study. The main resources to be monitored include:

1. the additional time for the procedure of PO screening and consultation/explanation, compared to current practice, during pregnancy (principally midwife and paediatrician time),
2. the equipment and resources associated with PO and knock-on costs associated with additional echocardiograms,
3. time and resources associated with clinical examination
4. neonatal cardiac surgery
5. admissions to neonatal intensive care.

Information on unit costs or prices will then be required to attach to each resource item in order that an overall cost per infant can be calculated. Cost data will be collected from two principal sources. First, the primary PO test accuracy study will provide the time (staff and equipment) and other resource use data to estimate cost incurred in administering the PO test and the knock on tests. Primary cost data for many of these resources will be collected from the participating hospital sites. Where possible other cost data, such as cost of midwife time etc to carry out the test will be collected from routine sources, including Netten *et al* (34) and hospital finance departments. Many cost data are already available in recently published sources. A study to investigate the costs of different levels of neonatal intensive care has already been carried out (35) and other cost studies with relevant costs and costs associated with pre term delivery are available to supplement these (36;37). Also recent systematic review and cost-effectiveness analysis on Newborn Screening For Congenital Heart Defects has been recently published (6). This study retrieved available literature costs and some primary costs which can be used as a comparison.

5.6. Data management and validation

5.6.1 Confidentiality of personal data

The study will collect personal data and sensitive information about the participating infants. Participants will be informed about the transfer of this information to the Pulse Ox study office at the University of Birmingham Clinical Trials Unit (BCTU) and will be asked to consent to this. Participant demographic data, test results and questionnaire answers will be stored on a secure server, inputted where possible via the internet using secure socket layer encryption technology. Remaining data will be returned by post to the BCTU. The use of the baby's NHS number will minimise the risk of disclosure of identifiable data. Data to be processed outside the BCTU, or cross-referenced with CARs, will be anonymised. Only registered study personnel will have access to the database.

All participant data will be processed and stored according to the MRC guidelines of use of personal data. All personal information obtained for the study will be held securely and treated as confidential. All staff, at the hospitals, in the community midwife teams or at the BCTU, share the same duty of care to prevent unauthorised disclosure of personal information. No data that could be used to identify an individual will be published.

5.6.2 Long-term storage of data

All participant data will be stored on computer for 20 years after recruitment in accordance with MRC guidelines on the archiving of personal medical data for research.

6. ACCRUAL AND ANALYSIS

6.1. Sample size

The approach used in the sample size calculations is to consider the power that a study of a certain size has for the lower limits of the confidence intervals for both sensitivity and specificity to exceed particular values (and hence prove that the test is statistically significantly superior to those values). Sample size computations have been undertaken assuming that the screening strategy will have a sensitivity of 75% and a specificity of 99.5%. Sample sizes for CHD prevalence between 2 and 5 per 1000 using a one-tailed significance level of 2.5% have been computed.

Simulations of the study design and analysis (using 10,000 repetitions) were performed to account for (1) sampling variability in the observed number of cases of CHD and (2) sampling variability in the observed sensitivity and specificity, and (3) to incorporate the use of binomial exact methods to estimate confidence intervals. Standard asymptotic sample size computations do not allow for all three of these issues to be considered simultaneously. Plots of power against the values of sensitivity and specificity that the study wishes to rule out were constructed for sample sizes of 10000, 15000, 20000, 25000, 30000 and 35000.

Based on these simulations it was observed that a sample size of 20,000 will have 80% power to demonstrate that sensitivity is above 61% at a prevalence of 5 per 1000 in the overall sample. For the subgroup of women who are not selectively screened antenatally, it is anticipated the prevalence to be around 2 per 1000, a level at which sensitivity of 52% can be detected with 80% power. If the sample size is increased to 25,000 the study will have 80% power to prove the sensitivity to be above 63% and 55% at 5 and 2 per 1000 CHD prevalences respectively; if it is increased to 30,000 the corresponding values are 64% and 57%. Variation of prevalence does not affect the power to detect differences in specificity. For sample sizes above 15,000 the study will have greater than 90% power to prove that the specificity is above 99.3%.

Further simulations using lower assumed values of the sensitivity and specificity for the screening strategy were undertaken. Statistical power to test absolute differences in sensitivity and specificity of the same magnitude was noted to be comparable to the above scenario for assumed values are within a reasonable range of those used above. Thus a sample size of 25,000 will have 80% power to prove that sensitivity is higher than a value 12% (prevalence 5 per 1000) or 20% (prevalence of 2 per 1000) below the assumed sensitivity of the test, and the specificity is above a value 0.2% below the assumed specificity.

The assumption about disease prevalence is quite conservative. A review of 62 prevalence studies since 1955 estimated a combined prevalence of 6 per 1000 live births of moderate to severe CHD (38). If prevalence in this study is higher than 0.5%, it will have more than the projected power to undertake subgroup analyses confidently. On this basis, considering the likely prevalence, the study aims to recruit a sample of 20,000 neonates.

6.2. Projected accrual and attrition rates

Accrual and attrition rates will be closely monitored against our target, and in the unlikely event that recruitment is insufficient, the Study Management Group have identified other maternity units likely to be able to participate.

6.3. Analysis for test accuracy study

The main analysis for diagnostic accuracy will include estimation of sensitivity, specificity, predictive values, likelihood ratios and their 95% confidence intervals. The baseline

characteristics of the patients enrolled in the study will be examined and planned subgroup analyses will be undertaken. Subgroup analyses are limited by statistical power and can produce spurious results particularly if many are undertaken. The recent literature review and consultation with obstetricians suggests that the accuracy of the index tests may vary according to risk factors (high risk history or antenatal suspicion on ultrasound) and timing of PO test. Therefore, secondary analyses will be limited to these subgroups only. The main and subgroup analyses are powered as outlined above based on conservative prevalence estimates. All estimates of accuracy for subgroups will be interpreted with appropriate caution.

As secondary analyses, the reference standard information obtained from echocardiography will be utilised to compare antenatal screening with PO. Such studies are commonplace in cancer research where invasive tests cannot be undertaken on those with low probability of disease. From such a design, it is possible to estimate the relative true (TPR) and false (FPR) positive rates of the two test strategies, but not the absolute sensitivity or specificity of either(39). It is also possible to estimate the trade-off between additional true positives and false positives related to the addition of PO to the standard screening programme (40). The statistical significance of the difference will be assessed using McNemar's test for paired data, and confidence intervals for the ratios computed using the methods of Cheng and Macalouso (41). The same approach can be utilised for comparing PO and clinical examination except that this analysis will be biased due to lack of blinding between the two tests. A "latent class" analysis, as described by Walter (42), will be used to estimate the sensitivity and specificity of the PO test and the antenatal screening from the screen positive study using only echocardiography as a reference standard. This approach involves an assumption of independence of test errors in the diseased and non-diseased groups, which will be tested as part of the investigation.

Using multivariable logistic regression analysis, predictive probabilities will be generated for various combinations of history, antenatal tests and oximetry results (43) Historical features to be included in the regression model will include gestational age (35-37, >37 weeks' gestation), antenatal scan findings, clinical examination (although this is likely to be affected by workup bias) and family history of CHD. In statistical terms, logistic modelling will aim to derive a diagnostic regression function, i.e. probability of CHD given test result. The analysis will be performed with presence or absence of CHD verified by reference standard as the binary dependent (outcome) variable. The models will allow a direct estimation of the post-test-combination disease probabilities that is needed for decision-making and for decision-analysis. Models of varying complexity may be compared through the familiar receiver operating characteristic (ROC) analyses. More importantly, the clinical situation where some information is already acquired, such as antenatal ultrasound or presentation with symptoms prior to undertaking PO, will be mirrored. In this way, for various index test results conditional disease probabilities will be generated directly taking into account any overlap of information that may exist between tests. This approach evaluates the extent to which the findings of the index tests add value to the babies' presentation. Its output is transparent, and is likely to enable production of simple clinical algorithms based on probabilities. The advantages of tackling diagnostic problems with logistic regression modelling are well known (44;45). The limitation associated with the regression approach lies mainly in its generalisability to other data sets or clinical practices. The recommended techniques, such as bootstrapping to enhance generalisability and estimate the amount of shrinkage will be applied for model validation (46;47). It is anticipated that the sample will comfortably meet the recommended events per variable rule to avoid overfitting the models (48-50) even if some data were missing. In a sensitivity analysis, missing data will be estimated by multiple imputation and maximum-

likelihood methods, as appropriate, to explore the potential bias and reduced statistical power associated with listwise deletion (51).

6.4. Handling missing data

Sensitivity analysis will be employed to explore the potential bias and reduced statistical power associated with listwise deletion of missing data, using multiple imputation and maximum-likelihood methods, as appropriate (52).

6.5. Economic analysis

There will be two components to the analysis: a within study analysis and a model-based analysis, the latter will seek to refine and develop the decision tree model used in the recently published HTA report by Knowles *et al*. (6) The model based analysis will allow projection of costs and benefits beyond the immediate screening study data. Data from the follow up assessment carried out at one year on those who screened positive will be available from the study. Data will be sought from the anomaly register for those who initially screened negative and were not further followed up by the study. The accuracy data on screening based on the PO, and the clinical examination will be collected directly from the current study. There is a potential source of bias arising from the fact that the discrete clinical examination results may not be blind to the results of the PO. However, effort will be made to interpret these data appropriately and record any known potential bias. The data collected in this study will refine the detection rate and other aspects of PO which can be used in an already existing model.

The model will consider treatment over total duration for an infant screened positive by PO and will include consideration of medical and/or surgical treatments provided in the longer term. The model-based analysis will adopt a short term outcome of 'cost per timely diagnosis of life-threatening CHD' and an outcome of cost per death avoided at one year to coincide with the final follow up. Depending on the data availability from published sources, the model outcome may be extended beyond the study outcome of one year. However, given that at present there is no consensus regarding the methodology for developing QALYs in children, a cost utility analysis will not be attempted (6).

6.5.1 Within study analysis

This will use only data collected within the accuracy study and so, for example, will draw upon the test performance data. Estimates of costs and benefits will therefore relate only to the period of follow-up, and no predictions for costs and benefits beyond the study will be made. The data available for this analysis will be patient-specific resource use and costs. Given the skewness inherent in most cost data and the concern of economic analyses with mean costs, we shall use a bootstrapping approach in order to calculate confidence intervals around the difference in mean costs (53;54). An incremental economic analysis will be conducted. The base-case analysis will be framed in terms of cost-consequences, reporting data in a disaggregated manner on the incremental cost and the important consequences, including data on the number of true positive cases of CHD detected, etc.

Three main strategies will be compared:

- Routine clinical examination alone
- PO screening as an adjunct to clinical examination
- PO alone

6.5.2 Discounting

If the outcome of the model coincides with that of the study, i.e. at one year, then discounting is not required. But if the model extends beyond the outcome of the study and given the potentially relatively long time horizons being considered in these analyses, many of the costs (and benefits) will be incurred (and experienced) in future years. Using discounting, adjustments will be made to reflect this differential timing. The base-case analysis will follow Treasury recommendations for public sector projects.

6.5.3 Presentation of results and sensitivity analysis

The results of these economic analyses will be presented using cost-effectiveness acceptability curves to reflect sampling variation and uncertainties in the appropriate threshold cost-effectiveness value. Both simple and probabilistic sensitivity analyses will be used 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.

7. DATA ACCESS AND QUALITY ASSURANCE

7.1. In-house Data Quality Assurance

7.1.1 Monitoring and Audit

Midwifery staff performing the PO tests will be trained by the lead research midwife, who will review their skills regularly. A sample of test results inputted in the maternity units will be cross-checked at the BCTU with paper records.

7.1.2 Statistical monitoring throughout the study

Real-time reports will be available to postnatal staff indicating missing test and questionnaire data for all participants at that centre. This will be supplemented by regular reminders from the Study Office for incomplete data. The study statistician will report on recruitment, compliance and completeness of verification to the Steering Committee quarterly.

7.2. Independent Supervision of the Study

The Study Steering Committee provides independent supervision for the study, providing advice to the investigators and the Sponsor on all aspects of the study and affording protection for patients by ensuring the study is conducted according to the MRC Guidelines for Good Clinical Practice in Clinical Trials.

If the clinical co-ordinators are unable to resolve any concern satisfactorily, collaborators, and all others associated with the study, may write through the study office to the chair of the SSC, drawing attention to any concerns they may have about the possibility of distortion of clinical practice, or of particular categories of patient requiring special study, or about any other matters thought relevant.

The study shall follow and comply with the MRC Guidelines on Good Clinical Practice, although its advice in relation to test accuracy studies is limited. The Study Team has made provisional recommendations regarding the independent supervision and data monitoring of test accuracy studies as a consequence of experiences in previous studies (55). One such recommendation is that, if desirable, the independent Data Monitoring and Ethics Committee (DMEC) should be formed as a sub-committee of the Study Steering Committee (SSC). For the purposes of this study, the SSC shall convene and nominate a three member independent DMEC from within its membership, that shall not include study researchers.

7.3. Data Monitoring and Ethics Committee: determining when clear answers have emerged

If the PO test has acceptable sensitivity and specificity, using echocardiography and clinical examination as a reference, then this may become apparent before the target recruitment has been reached. The assumed prevalence of CHD may prove to be inaccurate and require a recalculation of the sample size. Alternatively, the PO test may be found to be unworkable, new evidence of the effectiveness of the test might emerge from other sources or new technologies may be introduced to the market.

To protect against this, at 3-4 months into recruitment to the study, interim analyses of major endpoints will be supplied to the DMEC along with updates on results of other related studies, and any other analyses that the DMEC may request. The DMEC will determine whether the assumptions underpinning the sample size are correct at 3-4 months after commencement of recruitment. In particular they will be asked to examine the proportion of babies showing reduced oxygen saturation by PO and those who were diagnosed by antenatal scanning. The interim analysis will also determine if the principal question on index test accuracy has been answered and will monitor adverse events. The combined SSC/ DMEC will decide if the accuracy of the tests shows both (a) “proof beyond reasonable doubt”* that one particular test is definitely superior or definitely inferior in terms of a net difference in the major endpoints, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians. The SSC/DMEC can then decide whether to close or modify any part of the study. Unless this happens, however, the SSC, the collaborators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results.

8. ORGANISATION AND RESPONSIBILITIES

The Chief Investigator is responsible for the management, central co-ordination of clinical and administrative aspects of the study, compliance with the Research Governance Framework and management of study budget. Relevant ethics committee and Trust research governance approval will be coordinated centrally for efficiency and speed.

All investigators are responsible for ensuring that the research they undertake follows the agreed protocol, for helping care professionals to ensure that participants receive appropriate care while involved in research, for protecting the integrity and confidentiality of clinical and other records and data generated by the research, and for reporting any failures in these respects, adverse reactions and other events or suspected misconduct through the appropriate systems.

8.1. Centre eligibility

Initially, six hospitals in six NHS Trusts will recruit women into the study. These centres will receive equipment for the PO test from the study and will be funded to employ a part-time research midwife to conduct the study. Other centres wishing to participate can do so provided their Trust will supply the above resources.

8.2. Local Co-ordinator at each centre

Each Trust has a designated Consultant Neonatologist to act as Principal Investigator and bear responsibility for the conduct of research at their centre. Close collaboration between

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* Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least three standard deviations in an interim analysis of a major endpoint may be needed to justify halting, or modifying, the study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed.

midwifery and clinical teams is particularly important in order to ensure that recruitment of babies is maximised. The responsibilities of the Principal Investigators will be to ensure that all medical and post-natal ward staff involved are well informed about the study. This will involve distributing protocols and patient information sheets to all relevant staff, displaying publicity material where it is likely to be read, and contributing to the regular newsletters. The Principal Investigators should liaise with the study administrator on logistic, data collection and administrative matters connected with the study.

8.3. Midwifery Co-ordinator at each centre

Each participating centre will have a designated research midwife who will act as Local Midwifery Coordinator. This person would be responsible for ensuring that all eligible babies are considered for the study, that patients are provided with study information sheets, and have an opportunity to discuss the study if required. The midwife will be responsible for the organisation of data collection and will be the first point of contact for data queries.

8.4. The Study Office

The Study Office at the University of Birmingham Clinical Trials Unit (BCTU) is responsible for providing all study materials, including the coded stickers and questionnaires. Additional supplies of any printed material can be obtained on request. The Study Office is also responsible for collection and checking of data (including reports of serious adverse events) and for analyses. The Study Office will help resolve any local problems that may be encountered in study participation.

8.5. Research Governance

The conduct of the study will be according to the principles of MRC Guidelines for Good Clinical Practice in Clinical Trials (1998) and the appropriate NHS Research Governance Frameworks.

All centres will be required to sign an Investigator's Agreement, detailing their commitment to accrual, compliance, Good Clinical Practice, confidentiality and publication. Deviations from the agreement will be monitored and the SSC will decide whether any action needs to be taken, e.g. withdrawal of funding, suspension of centre.

The Study Office will ensure researchers not employed by an NHS organisation who interact with individuals in a way that has direct bearing on the quality of their care hold an NHS honorary contract for that organisation.

8.6. Regulatory and Ethical Approval

Site specific approval from local research ethics committees (LREC) will be gained for each site following Multi-centre Research Ethics Committee (MREC) approval. The LREC and Trust Research and Development Office will assess each site for "locality issues" relating to their population, the investigators, the facilities and resources.

8.7. Funding and Cost implications

The research costs of the study are funded by a grant from the NHS R&D Health Technology Assessment Unit awarded to the University of Birmingham.

The study has been designed to minimise extra 'service support' costs for participating hospitals, with no extra visits to hospital and no extra tests. Additional costs associated with the study should be minimal. These costs should be met by accessing the Trust's budget.

8.8. Indemnity

There are no special arrangements for compensation for non-negligent harm suffered by patients as a result of participating in the study. The study is not an industry-sponsored

study and so ABPI/ABHI guidelines on indemnity do not apply. The normal NHS indemnity liability arrangements for research detailed in HSG96(48) will operate in this case.

However, it should be stressed that in terms of negligent liability, NHS Trust hospitals have a duty of care to a patient being treated within their hospital, whether or not that patient is participating in a clinical study. Apart from defective products, legal liability does not arise where there is non-negligent harm. NHS Trusts may not offer advance indemnities or take out commercial insurance for non-negligent harm.

8.9. Publication

A meeting will be held after the end of the study to allow discussion of the main results among the collaborators prior to publication. The success of the study depends entirely on the wholehearted collaboration of a large number of doctors, midwives and others. For this reason, chief credit for the main results will be given not to the committees or central organisers but to all those who have collaborated in the study. Collaborators will be permitted to publish data obtained from participants in the Pulse Ox Study that use study outcome measures but do not relate to the study objectives.

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APPENDIX A PATIENT INFORMATION SHEET:

Pulse Ox STUDY PULSE OXIMETRY AS A SCREENING TEST FOR CONGENITAL HEART DISEASE IN NEWBORN BABIES

We would like to invite you to take part in a research study that may help newly born babies. The decision to take part will be yours, you do not have to join in or give us the reason why you choose not to. It is important for you to understand why the research is being done and what it will involve. Discover more by reading the following information. Feel free to spend time discussing it with anyone - it may help to talk to your midwife, or a member of the research team. You will have plenty of time to decide whether or not to take part.

What is the purpose of the study?

- Congenital Heart Disease (CHD), where the baby's heart is abnormal at birth, is the most common group of abnormalities in newborn babies and affects 7-8 per 1000 births.
- If some heart problems are not diagnosed early, they can very quickly cause the baby to become unwell
- Timely recognition of these heart defects is vital in order to improve outcome.
- Currently in the UK, all newborn babies undergo a routine examination, usually in the first 24 hours after birth, during which, among other things, a careful assessment of the heart is undertaken. ***However, it is estimated that over half of all babies with CHD will not be picked up by this examination.***
- Pulse Oximetry is a simple test which has been used routinely used on babies in the Neonatal Unit for many years.
- Pulse Oximetry measures the amount of oxygen being carried around in the blood by shining a special light through the skin of the babies' hand and foot. ***It is completely harmless and painless and takes only a couple of minutes to perform.***
- This test will pick up babies who do not have as much oxygen in their blood as they should and this is a common finding in the early stages of Congenital Heart Disease
- This hospital is now hoping to screen every newborn baby with pulse oximetry as a way of trying to detect those with heart problems before they become unwell.
- We do not know for certain how accurate this method will be at detecting heart problems - that is why we are undertaking this research study.
- **We do know that it is important to identify babies who have low oxygen levels and find out what is causing this.**

Commonly asked questions

Why have I been chosen?

All women being booked in for antenatal care at this hospital are being invited to take part. It is hoped 20,000 women from seven hospitals will take part in the study.

Do I have to take part?

It is up to you to decide whether or not to take part. You should keep this information sheet and consent form in your hand-held notes as you will be asked at your antenatal clinic

whether you are willing to take part. If you agree, you will be asked to sign the consent form. At the time of testing, you will be asked again if you still agree to participate. You are free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to be tested, will not affect the standard of care you receive.

What will happen to me if I take part?

If you agree to take part, we will perform the pulse oximetry test on your baby. We will do this before s/he is 24 hours old, preferably at around 3-6 hours of age. Two readings will be taken: one from the hand and one from the foot. **The test will take no more than five minutes to perform.**

We know from our experiences with babies on the neonatal unit what level of oxygen in the blood is acceptable.

If your baby has acceptable oxygen levels no further action will be taken and your baby will be managed as usual.

If your baby's oxygen measurement is below this level it may be for one of the following reasons.

1. The baby's circulation is still readjusting to the process of birth - this is quite common. The baby does not have a problem with the heart or lungs.
2. Your baby has a problem with the lungs which means not enough oxygen is getting into the body.
3. Your baby has a problem with the heart which means that not enough oxygen is getting around the body.

If your baby's oxygen measurement remains low then s/he will be carefully examined for signs of a problem with the heart or the lungs.

If we find a problem or if the oxygen measurement does not improve, then the baby will need further tests to find the cause – this will include a scan of the heart (echocardiogram) to look for congenital heart disease. Your doctor will explain exactly what this means for your baby and what will happen. We will use data from the echocardiogram and clinical follow up, and up to one year after birth, we will search regional databases for all babies with heart disease. We will compare this information with data from the oxygen measurement.

A low oxygen measurement does not necessarily mean your baby has a problem. It just means that they are more likely to – further tests will help us identify which babies have problems and which do not. If your baby has a low oxygen measurement and then the follow up tests are normal, this means your baby's heart is normal.

However, an acceptable oxygen measurement does not *completely exclude* other problems including heart disease.

What else do I have to do?

We (the researchers) would also like a sample of mothers to answer some questions of acceptability. You may be given an anonymous questionnaire to complete before you leave hospital. We want to find out the how you found the tests and the research study, the information given to you before the test, and the way you were given your test results.

What are the possible disadvantages and risks of taking part?

We have lots of experience with this test in babies on the Neonatal Unit and we do not expect there to be any problems or risks to the babies who take part.

What are the possible benefits of taking part?

There may be no benefit from taking part, however, we hope that a heart or lung problem would be detected early which would ensure that treatments for the disease could be started earlier.

Also, of course, the information we get from this study may in the future help us better treat newborn babies.

What if something goes wrong?

We do not believe that there is a risk of anything going wrong. However if your baby is harmed by taking part in this study, there are no special compensation arrangements. If your baby is harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

Will my taking part in this study be kept confidential?

Yes, all information collected in the study will remain strictly confidential in the same way as your other medical records. If you agree to take part, your midwife or doctor will send basic information about you and your baby to the study's central organisers. This information will be put into a computer and analysed. The questionnaires will be identified only by a code number and will not be seen by your doctor or midwife. All information will be held securely and in strict confidence. No named information about you will be published in the study report. Occasionally, inspections of clinical study data are undertaken to ensure that, for example, all participants have given consent to take part. But, apart from this, only the study organisers will have access to the data.

What will happen to the results of the research study?

The study will last for around two and a half years, after which we expect to publish the results in scientific journals.

Who is organising and funding the research?

The Pulse Ox study is funded by a grant from the National Health Service's Health Technology Assessment programme. The central study organisers are based at the University of Birmingham. The Clinical Trials Unit at the University of Birmingham will collect and analyse the data. The researchers, doctors and midwives involved are not being paid for recruiting women into the study. We cannot pay women to take part either, but we will be very grateful for their help in finding out more about the accuracy of this new test.

Do you have any other questions?

Having read this leaflet, we hope that you will choose to take part in the Pulse Ox Study. If you have any questions about the study now or later, feel free to ask your midwife. Their name and telephone numbers are given on the front of this leaflet.

What if I have any concerns?

If you have any concern or other questions about this study or the way it has been carried out, you should contact the investigator [name], or you may contact the [name] hospital complaints department.

APPENDIX B: PATIENT CONSENT FORM:

Pulse Ox STUDY

SCREENING TEST FOR CONGENITAL HEART DISEASE IN NEWBORN BABIES

I confirm that I have read and understand the information sheet (version 1.1, dated 22/06/2007) for the above study and have had the opportunity to ask questions. ☐ (Please initial)

I understand what is involved in the Pulse Ox study and agree to participate. I intend to participate in the study, but I understand that I am free to change my mind when I go into hospital without necessarily giving a reason. If I do withdraw, I can continue to expect the highest standard of care from my doctor or midwife. ☐ (Please initial)

I understand that the information will be used for medical research only and that I will not be identified in any way in the analysis and reporting of the results. I understand that sections of any of my medical notes may be looked at by responsible individuals from the University of Birmingham or from regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐ (Please initial)

DURING PREGNANCY

I consent to participate in the Pulse Ox Study ☐ (Please initial)

AT TIME OF PO TESTING

I still agree to participate in the Pulse Ox Study (midwife to indicate here) ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Copies should be kept in hand-held notes until after delivery, then top copy should be kept in the mother's notes, pink copy put in the study collection box and the yellow copy given to the mother to keep.

APPENDIX C: SERIOUS ADVERSE EVENT FORM

Please report any **serious**, **unexpected** adverse events[2] believed to be due to the treatments given as part of the Pulse Ox study by sending or faxing the following details to the Pulse Ox Study Office (fax: 0121-415-9136) within 2 weeks of the event:

Patient's Full Name: .....

Date of Birth: ..... Hospital Number: .....

Responsible doctor: .....

Date Treatment Started:(if known) .....

Date Event Started: ..... Date Event Ceased: .....

Outcome (e.g. fatal, recovered, continuing): .....

Details of Adverse Event (please attach copies of relevant reports) .....

.....

.....

.....

Did the event require or prolong hospitalisation? .....

Please give reasons why you consider the event to be treatment-related: .....

.....

.....

Name of Person Reporting (please print) .....

Telephone Number: ..... Today's Date: .....

[2] For the purposes of this study, "**serious**" adverse events are those which are fatal, life-threatening, disabling or require hospitalisation. "**Unexpected**" adverse experiences are defined as those that would not be expected as a result of PO testing. It is not required to report in this way side-effects or events that might reasonably be expected.

APPENDIX D: PULSE OX STUDY DATA COLLECTION FORM

Section 1: Eligibility

Is the baby well? Yes ☐ No ☐

*If the baby is **well**, they are **eligible** for the study. Please ensure consent has been taken and continue with **sections 2 – 5 below.***

*If the baby is **not well**, they are **not eligible** for the study. Please complete the '**Ineligibility Form'**, put in the participant pack and put it in the Pulse Ox collection box. Treat the baby as normal.*

Section 2: Identifying Details

Baby Hospital Number ☐☐☐☐☐☐☐☐☐☐

Baby **NHS** number ☐☐☐☐☐☐☐☐☐☐

Baby date of birth _____ / _____ / _____

Time (24hr) _____ : _____

Male ☐ Female ☐

Gestational age _____ /40 weeks

Mother's Forename _____

Mother's Surname _____

Hospital Number ☐☐☐☐☐☐☐☐☐☐

Mother's NHS Number ☐☐☐☐☐☐☐☐☐☐

Mother's date of birth _____ / _____ / _____

(or attach sticker)

Mother's gravida _____ parity _____

Section 3: Language

Was a translator and/or a translated version of the Information Sheet and Consent required? Yes ☐ No ☐

If yes, specify language: _____

Section 4: Pulse Oximetry Saturations

First reading (This should be taken within 24 hours of age or before discharge)

Performed in: Delivery Suite ☐ Post Natal Unit ☐ Neonatal Unit ☐

Performed by:

PRINT NAME: _____

Doctor ☐ Nurse ☐ Midwife ☐ Midwifery Assistant ☐ Care Assistant ☐ Neonatal nurse ☐

Date	Time	Foot sats (%)	Right hand sats (%)	% difference	Pass/Refer

*If the result is normal (i.e. **Pass**), nothing further needs to be done. Please **ensure sections 1-5 are completed**. Please put this form in the participant pack and put it in the Pulse Ox collection box.*

*If less than 95% in either limb or ≥3% difference between limbs, this is a **Refer**, the baby needs to be examined/ reviewed by someone trained in neonatal examination. **Please continue with section 6 overleaf.***

Section 5: Antenatal Diagnosis

Is there a family history of congenital heart defects? Yes ☐ No ☐

Was CHD suspected on antenatal ultrasound? Yes ☐ No ☐

The following sections only need to be completed if the first pulse oximetry reading was <95% in either limb or ≥3% difference between limbs i.e. a Refer.

Section 6: Clinical Examination

Undertaken by: Nurse/ Midwife ☐ SHO/ Registrar ☐ Consultant ☐ Other ☐

How long did the exam take? _____ minutes

Did the baby show signs of CHD at examination? Yes ☐ No ☐

If yes, was this murmur ☐ cyanosis ☐ abnormal pulses ☐

Overall exam finding Normal ☐ Abnormal ☐ Details:_____

*If **exam is normal**, a second PO reading needs to be taken. This should be taken 1-2 hours after the first reading. **Please complete section 7 below.***

*If **exam is abnormal,** the baby needs to be referred straight to the Neonatal team for further investigation and management. A second PO reading does not need to be taken. **Please continue with sections 9-14 overleaf.***

Section 7: Second Pulse Oximetry Reading

Performed in: Delivery Suite ☐ Post Natal Unit ☐ Neonatal Unit ☐

Performed by:

PRINT NAME: _____

Doctor ☐ Nurse ☐ Midwife ☐ Midwifery Assistant ☐ Care Assistant ☐ Neonatal nurse ☐

Date	Time	Foot sats (%)	Right hand sats (%)	% difference	Pass/Refer

*If less than 95% in either limb or ≥3% difference between limbs, this is a **Fail**, the baby needs to be referred to the Neonatal team for further investigation and management. **Please continue with sections 8-14 overleaf.***

*If the result is normal (i.e. **Pass**), nothing further needs to be done. Please ensure all above sections are completed. Please put this form in the participant pack and put it in the Pulse Ox collection box.*

The following sections only need to be completed if the clinical examination found an abnormality or if the second pulse oximetry reading was a <u>Fail</u> and the baby has been referred to the Neonatal team for further investigation and management.

Section 8: Hyperoxia Test *(only to be completed if second PO reading was a fail)*

Performed by: Nurse ☐ SHO ☐ Registrar ☐ Consultant ☐

Did saturation increase to 95% or above? Yes ☐ No ☐

Section 9: Clinical Symptoms

If baby showed signs of CHD at birth, describe

Collapse ☐ Cyanosis ☐ Acidosis ☐ Respiratory distress ☐

Did this baby have a respiratory illness or any illness other than CHD?

Yes ☐ No ☐ If yes details: _____

Section 10: Echocardiography

Date of echocardiography ____ /____ /____ Time____ : ____ (24 Hour)

Echocardiographer: Cardiology Research Fellow ☐ Other Echocardiographer ☐

Result: Normal ☐ Abnormal ☐ Uncertain ☐

Details: _____

Section 11: Review of Echocardiography

Reviewed by: Cardiology Research Fellow ☐ Consultant ☐ Other ☐ (Please tick more than one box if applicable)

Date of review ____ / ____ / ____

Result: Normal ☐ Abnormal ☐ Uncertain ☐

Details: _____

*If there is a **disagreement between the two results** <u>or</u> the **result of the review is uncertain**, a second echocardiogram needs to be performed. This will be done by a Consultant Paediatric Cardiologist at Birmingham Children's Hospital*

Date of second echocardiography ____ /____ /____

Result: Normal ☐ Abnormal ☐ Details: _____

Please continue with sections 12-14 overleaf.

Section 12: Admission Summary

Number of days on Postnatal unit? _____ days

Number of days on Neonatal unit? _____ days

Section 13: Discharge Details

Home ☐ Cardiac Unit ☐ Other ☐ Details: _____

If home, date of discharge _____ / _____ / _____ Time of discharge (24hr) _____ : _____

If cardiac unit, number of days on unit _____ days

Section 14: Death Details

Death ☐ Date of death _____ / _____ / _____ Time of death (24hr) _____ : _____

Cause of Death: Cardiac ☐ Non-cardiac ☐

If cardiac: Post-operative ☐ Other ☐ If other, please specify: _____

If non-cardiac, please specify: _____

PULSE OX STUDY

CONGENITAL HEART DEFECT CASE REPORT FORM

Date of Diagnosis _____ /_____ /_____

How was the CHD detected and confirmed?

- Pulse oximetry at birth then echocardiogram ☐
- Clinical examination at birth then echocardiogram ☐
- Post-mortem ☐
- Later echocardiogram by paed cardiologist ☐
- Congenital anomaly registry ☐

Type of CHD?

Aortic (valve) stenosis	☐	Persistent (patent) ductus arteriosis	☐
Atrial septal defect	☐	Tetrology of Fallot	☐
Coartation of aorta	☐	Total anolomous pulmonary venous connection	☐
Complete artioventricular septic defect	☐	Transposition of great arteries	☐
Hypoplastic left heart syndrome	☐	Ventricular septal defect	☐
Interruption of aortic arch	☐		

Other (specify) _____

Has the baby had cardiac surgery? Yes ☐ No ☐ Planned ☐

If yes, when was the surgery _____ /_____ / _____

Type of surgery? _____

Death ☐ Date of death _____/_____/_____ Time of death (24hr) _____ :_____

Cause of Death: Cardiac ☐ Non-cardiac ☐

If cardiac: Post-operative ☐ Other ☐

If non-cardiac, please specify: _____

APPENDIX E: DEFINITIONS OF ECHOCARDIOGRAPHIC FINDINGS

Normal	No echocardiographic abnormalities
Non- Significant	No clinical signs (e.g. murmur, thrill, pulse abnormalities, hepatic enlargement) No symptoms Small patent ductus arteriosis (PDA) or small inter-atrial communication (patent foramen ovale (PFO), atrial septal defect (ASD) or muscular ventricular septal defect (VSD)) Mildly abnormal turbulence at branch Pulmonary Artery Echocardiographic findings no longer detected at 6 months
Significant	Small patent ductus arteriosis (PDA) or patent foramen ovale (PFO) or muscular ventricular septal defect (VSD) Mildly abnormal turbulence at branch Pulmonary Artery Above where echocardiographic findings persist for longer than 6 months of age Any cardiac lesion which requires regular monitoring beyond 6 months or drug treatment but does not fall into serious or critical category.
Serious	Any cardiac lesion not defined as critical which requires intervention (cardiac catheterisation or surgery) within 1 year of age
Critical	All infants with hypoplastic left heart, pulmonary atresia with intact ventricular septum, simple transposition of the great arteries or interruption of the aortic arch and all infants dying or requiring surgery within the first 28 days of life with the following conditions: coarctation of the aorta, aortic valve stenosis, pulmonary valve stenosis, tetralogy of Fallot, pulmonary atresia with ventricular septal defect, or total anomalous pulmonary venous connection.

APPENDIX F: ACCEPTABILTY QUESTIONNAIRE: NEONATOLOGY GROUP

- What is your role? (if your job has changed, please give your role at the time of the study?) (tick box(es)).

  Neonatologist (consultant) □

  Echocardiographer □

  Senior House Officer □

  Registrar □

- To what extent do you think that pulse oximetry has been worthwhile?
- How effective do you think pulse oximetry testing is?
- How did the pulse oximetry assessment affect your role?
- How do you think the women felt about having taken part in the study?
  - To what extent do you think they felt it was worthwhile?
- Did you encounter any incidents where there were problems in connection with having had the test carried out? (yes/no)
  - If so, please give details below.
- Did you encounter any incidents where having the test proved beneficial? (yes/no)
  - If so, please give details below.
- How would you feel if the study showed pulse oximetry to be beneficial and working with test results became a routine part of your job?
- What do you think the benefits of pulse oximetry have been?
- What do you think the costs of pulse oximetry have been?
- How your thoughts about pulse oximetry have changed over time:
  - How did you feel about the test at the start of the study? (or the start of your placement)
  - How do you feel about the test now? What is it that makes you feel that way?
- In general, how do you feel about the use of monitoring equipment for new-born babies?

APPENDIX G: STAFF EMAIL SURVEY INFORMATION SHEET

What is the purpose of the study?

In the Pulse Ox study, more than 20,000 new born babies were screened for congenital heart disease using pulse oximetry. Pulse Ox aims to determine the accuracy and cost effectiveness of the test, and to assess the psychosocial effect of the screening for parents. It is important to understand the experience of health care professionals, such as those receiving tested babies in neonatology, whose work has been affected by the study and to determine whether the test is acceptable to them also.

Why have I been chosen?

You have been invited to take part in this email survey because, in your role, you are likely to have encountered babies who had the pulse oximetry test as part of the Pulse Ox study. We are inviting staff in the neonatology units of all six hospitals taking part in the Pulse Ox study to complete this survey.

What will happen to me if I take part?

You will be asked to complete a short survey by email. The survey will include items such as how pulse oximetry affected your role and whether or not you consider the test to be beneficial. The researcher (Rachael Powell) will collate a summary of the comments raised. This summary will be emailed back to you and you will be invited to comment on its contents. For example, if someone has raised an issue that you had not considered, or that you disagree with, you will be able to respond.

Summaries will be created for groups of staff with similar roles. So, for example, if you are a Senior House Officer (SHO), your responses will be summarised with other SHOs' comments and will be emailed only to the SHO group for further comment.

Only the researcher (Rachael Powell) will know who made which comment; no comment will be directly emailed to the group.

Are there any potential risks in talking part in the study?

It is not expected that there are any risks to you in taking part in the study.

Do I have to take part?

Whether or not you take part is completely up to you. If you do choose to take part, you are free to withdraw at any time, without giving a reason.

Will my taking part in this study be kept confidential?

Taking part in this study is completely confidential. None of your colleagues will know who made which comment. Only members of the research team will have access to returned surveys. When we write up the results it will not be possible to identify anything that you tell us as being about you. All data will be kept in a locked filing cabinet or in password-protected computer files. Data will be stored at Aston University for 10 years and then destroyed.

What will happen to the results of the research study?

When the study is complete, the findings will be written up as part of the Pulse Ox study report to the Health Technology Assessment programme. They will also be written up and submitted for publication in scientific journals. **You will not be identifiable in any of these documents.**

Who is organising and funding the research?

The Pulse Ox study is funded by a grant from the National Institute of Health Research Health Technology Assessment programme to researchers at the University of Birmingham and Aston University. This email survey is being organised by Dr Rachael Powell and Dr Helen Pattison from Aston University, as part of the Pulse Ox study.

Who do I Contact if I need Further Information?

For further information about the email survey contact:

Dr Rachael Powell
Psychology
School of Life and Health Sciences
Aston University
Aston Triangle
Birmingham, B4 7ET.

Email: r.k.powell@aston.ac.uk
Phone: 0121 204 4188

APPENDIX H: FOCUS GROUP STAFF INFORMATION SHEET

What is the purpose of the study?

In the Pulse Ox study, more than 20,000 new born babies were screened for congenital heart disease using pulse oximetry. Pulse Ox aims to determine the accuracy and cost effectiveness of the test, and to assess the psychosocial effect of the screening for parents. It would not have been possible to screen these babies without the support of the staff who carried out the tests. It is important to understand the experience of health care professionals whose work has been affected by the study and to determine whether the test is acceptable to them also.

Why have I been chosen?

You have been invited to take part in this group discussion because you have been involved in carrying out the test on new born babies.

What will happen to me if I take part?

You will be asked to take part in one group discussion. The other people in the group will be colleagues who have also carried out the test. The researchers (Dr Rachael Powell and Dr Helen Pattison) will ask you to discuss your experiences of using the test, how it has affected your role at work and your views about testing neonates more generally. The discussion will last up to one hour and will be recorded on a digital voice recorder.

Are there any potential risks in talking part in the study?

It is not expected that there are any risks to you in taking part in the study.

Do I have to take part?

Whether or not you take part is completely up to you. If you do choose to take part, you are free to withdraw at any time, without giving a reason.

Will my taking part in this study be kept confidential?

Taking part in this study is completely confidential. Only members of the research team will listen to the recording or see the discussion transcripts. When we write up the results it will not be possible to identify anything that you tell us as being about you. All recordings and transcripts will be kept in a locked filing cabinet or in password-protected computer files. The voice recordings will be transcribed anonymously. As soon as we have written up the results, the voice recording will be destroyed and only the anonymous transcripts will be kept. These will be stored at Aston University for 10 years and then destroyed also.

What will happen to the results of the research study?

When the study is complete, the findings will be written up as part of the Pulse Ox study report to the Health Technology Assessment programme. They will also be written up and submitted for publication in scientific journals. **You will not be identifiable in any of these documents.**

Who is organising and funding the research?

The Pulse Ox study is funded by a grant from the National Institute of Health Research Health Technology Assessment programme to researchers at the University of Birmingham and Aston University. These group discussions are being organised by Dr Rachael Powell and Dr Helen Pattison from Aston University, as part of the Pulse Ox study.

Who do I Contact if I need Further Information?

For further information about the discussion groups, contact:

Dr Rachael Powell
Psychology
School of Life and Health Sciences
Aston University
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