Designing a cost-effectiveness decision analysis model of Pulse Oximetry screening: key considerations, challenges, and evidence requirements

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Ethical considerations

No ethical approval was required for this research.

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Abstract

Objectives

Decisions about population screening require consideration of whether individual and healthcare system benefits outweigh harms, and whether the opportunity cost of screening is justified by the overall benefits it generates. Developing cost-effectiveness models for screening interventions is complex. This paper outlines the processes, challenges, and required evidence generation to create a decision model of pulse oximetry (PO) screening for well appearing newborns.

Methods

We build on an existing approach to model conceptualisation for public health interventions, applying it to screening of PO for hypoxaemia. Our process includes: iterative stakeholder consultation; development of criteria to determine key drivers of test value, and identification of data requirements, potential sources of evidence and research to fill evidence gaps.

Results

Our iterative consultation revealed heterogeneity in PO delivery and interpretation. Stakeholders agreed that impacts among newborns without cardiac conditions were drivers of test value. Diagnostic accuracy was available for detection of critical congenital heart disease (cCHD), but evidence on other detectable conditions, changes in time to diagnosis, treatment and health outcomes was lacking. We identified linkage of routine datasets and further analysis that could address evidence gaps.

Conclusions

We outline three areas of challenges for model conceptualisation in PO screening: Lack of evidence to characterise the pathway from screening to diagnosis to treatment; generalisability of evidence to how a test is implemented in a health system; and cognitive biases that influence stakeholders. To justify further research to address these challenges, an important consideration is whether the information value would exceed research costs.

Key messages

What is already known on this topic: Previous cost-effectiveness analyses of Pulse Oximetry have focussed on one specific element of the impact of screening without consideration of the full range of costs and consequences.

What this study adds: We conceptualise a model and clarify the requirements to undertake a cost-effectiveness analysis of pulse oximetry for hypoxaemia, thereby broadening the evaluation beyond critical congenital heart disease.

How this study might affect research, practice or policy: Previous consideration of pulse oximetry screening by the National Screening Committee in the UK has been hampered by a lack of suitable cost-effectiveness evidence. By directly working with commissioners, clinicians, and academics, this study provides clarity on the future design and implementation of a more complete assessment of the value for money of pulse oximetry screening than has been possible to date.
1. Introduction

Screening tests aim to identify disease before they become symptomatic. The information provided by screening could lead to improved health outcomes for individuals and health system savings if preventive or early treatment is more beneficial and/or less costly than treatment after symptomatic detection. However, screening tests can impose additional costs without compensating benefit if the results of the test do not alter treatment pathways, or if they result in inappropriate care for those falsely identified by the test. Screening tests incur healthcare resource use through the cost of the test, and in how they impact on subsequent care decisions. Deciding whether to implement screening requires consideration of whether the benefits to screened individuals outweigh the harms, and whether the opportunity cost of delivering the screening programme is justified by the overall benefits of screening[1].

The balance between the costs and benefits of a screening test can be assessed using cost-effectiveness analysis. Cost-effectiveness analyses of screening interventions are often model based in order to capture the entire time period from screening to final health outcomes, and to combine relevant evidence from a range of sources. Models must capture the key cost and outcome drivers that explain the difference between the introduction of a new screening test and comparator options such as alternative screening modalities or leaving current standard of care unaltered.

This paper presents an overview of the process to conceptualise a cost-effectiveness model for the use of pulse oximetry (PO) as a universal screening test in well appearing newborns in the UK. PO is a quick, non-invasive test that measures the concentration of oxygen in the blood using a sensor applied to the hand or foot. PO has been on the UK National Screening Committee’s formal agenda since 2012 when it was proposed as an additional screening test within the existing Newborn Physical Examination (NIPE) Programme[2]. The NIPE Programme screens new-born babies within 72 hours of birth, and then once again between 6 and 8 weeks for conditions relating to their heart, hips, eyes, and testes. PO has sometimes been utilised as one of a number of screening activities within a wider critical congenital heart defects (cCHD) screening and management pathway. However, given its mode of action, it has been suggested that the main value of PO may be as a screening test for hypoxaemia, a symptom of a range of conditions of which cCHDs are a subset[3]. These conditions include neonatal sepsis, pneumonia, persistent pulmonary hypertension of the newborn (PPHN), respiratory distress syndrome, pneumothorax, and transient tachypnoea of the newborn (TTN).

Building on a conceptual modelling framework of model development for decision problems in public health[4], a review of previous decision models in PO screening, and insight gained from iterative stakeholder consultation, we conceptualise a model and clarify the requirements to undertake a cost-effectiveness analysis of PO for hypoxaemia, thereby broadening the evaluation beyond critical congenital heart disease. We further outline criteria to include further broadening of diagnosis in the decision model and the implied evidence requirements to populate the conceptualised model.

2. Methods

Literature review
To begin model conceptualisation, a literature review was conducted to identify previous cost-effectiveness models developed to assess screening interventions in newborns, including: heart defects (CHD), circulatory, and breathing problems. We searched MEDLINE, EMBASE and the International HTA Database for articles published from 1st January 2000 and 15th October 2020 to identify economic evaluations of newborn screening or PO in new-born infants (see Appendix for full search strategies). Articles were sifted by title and abstract to identify relevant economic evaluations. Initial inclusion criteria were: 1) Based in an upper/middle income country, 2) Original research, 3) Considers both costs and outcomes. National Institute for Health and Care Excellence (NICE) clinical guidelines and Public Health England (PHE) reports were also searched for any economic evaluation of neonatal screening.

**Stakeholder consultation**

To understand how those using and receiving the test perceive its potential value and gain insight on the UK newborn screening pathway, an iterative consultation process was undertaken with neonatologists, paediatricians, nurse specialists, commissioners, and lay representatives with lived experience. Consultation consisted of three stages:

(i) An initial workshop to discuss the intention of the project, the results of the literature review and the relevant evidence and considerations for the decision problem;

(ii) A second workshop to discuss specific proposals for a conceptual model structure developed as a result of the literature review and first workshop;

(iii) A follow up survey to widen engagement to those who could not attend the workshops, and to refine key elements of the proposed model structure.

**3. Results**

**Literature review**

Out of 2458 identified articles, 46 met the inclusion criteria, ten of which were economic evaluations of PO screening [5-14]. Of these, two [5, 8] used preference-based outcomes i.e. quality adjusted life year (QALY) and disability adjusted life year (DALY), that are suitable for the decision-making context. One study used life years as the health outcome [10]. The remaining articles used clinical outcomes e.g., cost per additional newborn with congenital heart disease detected, that are not suitable for determining the value of PO screening relative to other NHS activities. All ten studies evaluated the use of PO screening as a test for congenital heart defects only. While the evaluations of PO screening excluded non-cCHD diagnoses such as pneumonia and sepsis, the review included one study relating to a blood test for sepsis.

The search identified 36 evaluations of other newborn screening programmes that calculated cost per QALY, DALY, or life year [15-50]. Of these, 25 evaluated a screening programme in which only one disease (e.g., cystic fibrosis) was investigated [15-19, 21-26, 28, 29, 31-33, 36, 39, 42, 45-50]. The remaining 11 evaluated screening for inborn metabolic disorders in which multiple disorders were screened for from one investigation [20, 27, 30, 34, 35, 37, 38, 40, 41, 43, 44].

The PO model used in Mukerji [5] was deemed to represent the best starting point for a new modelling analysis as it explicitly modelled the clinical pathway with a decision tree and also considered long-term health outcomes using a Markov model.
Stakeholder consultation process

The first stakeholder workshop consisted of neonatologists, a paediatric cardiologist, a lay representative with relevant lived experience, and a neonatal nurse practitioner. We posed the following questions and encouraged free discussion amongst the group:

1. How might the introduction of PO screening alter the experience of babies and their families?
2. What additional information does the result of PO screening provide in the context of other checks and tests provided in antenatal and postnatal care?
3. How might the information provided by PO screening change decisions about discharge, diagnostic work up, treatments etc.?

The second workshop consisted of the smaller stakeholder group plus additional neonatologists, paediatricians, nurse specialists, commissioners, and lay representatives. The workshop included presentations from the study team and polling to determine initial consensus among the 25 attendees. The discussion was structured around the Population, Intervention, Control, Outcome (PICO) framework for the decision problem and the key elements relevant for model conceptualisation. These were:

1. Baseline risk in babies subject to screening
2. Timing and modality of test
3. Screen positive pathways
4. Long term health

The follow up survey consisted of three themes:

1. The definition of the question to be addressed, in terms of a PICO framework
2. A proposed model structure
3. Data requirements and availability

We obtained 17 responses to the survey, who self-identified as clinical stakeholders (10), patient representatives (1), policy makers (3), researchers (2) and other (1).

The potential for heterogeneity in the way PO is delivered and interpreted was identified from the stakeholder feedback, which is summarised thematically in Table 1.
<table>
<thead>
<tr>
<th>Theme</th>
<th>Summary of stakeholder feedback</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Well appearing babies born after 37 weeks gestation without a ‘red flag’ are the target population for universal screening. Where clinical concerns are raised that the baby may be unwell based on other factors, the new-born would exit the universal screen pathway, but PO may still be provided as an investigative procedure.</td>
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<td></td>
<td>Subgroups should be considered within the overall population based on factors that constrain timing of the test (home birth and early discharge), maternal risk factors (e.g. diabetes) and newborn risk factors (e.g. the results of antenatal screening).</td>
</tr>
<tr>
<td><strong>Intervention - how PO will be delivered in practice</strong></td>
<td>The precise timing of the screen may vary between centres within a window of 6-24hrs.</td>
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<td></td>
<td>Most places deliver PO with two measurements, one with a sensor applied to the hand (pre-ductal) and one with the sensor applied to the foot (post-ductal), and this is regarded as best practice. In some places a single, post-ductal reading is taken.</td>
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<td></td>
<td>A single reading below 90% is generally regarded as indicative of urgent need for further investigation.</td>
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<td></td>
<td>The threshold may be as high as 96% to define a positive result.</td>
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<td></td>
<td>Where pre- and post-ductal measurements are taken, a second criteria determines a positive result if the difference between the two measurements exceeds a predefined threshold, often 2% or 3%.</td>
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<tr>
<td></td>
<td>Timing of the screen for hospital births is constrained by discharge of the mother and the newborn.</td>
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<td></td>
<td>Timing of the screen for home births is constrained by the timing and duration of the midwife visit.</td>
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<td></td>
<td>The number of PO screens performed can vary between units, and according to the results of the first screen.</td>
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<td></td>
<td>Introducing PO would not impact the rest of the screening pathway</td>
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<tr>
<td><strong>Post screen pathway</strong></td>
<td>Newborns who record very low oxygen readings (&lt;90%) or who develop symptoms after the screen will be admitted to neonatal care units.</td>
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<tr>
<td></td>
<td>If babies who are born at home screen positive, they need to be admitted to hospital.</td>
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<tr>
<td></td>
<td>Asymptomatic newborns that screen positive in hospital with a reading between 90 and 95% will be placed under observation, and a repeat screen may be performed within 1-2 hours of the initial screen.</td>
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<td></td>
<td>In transitional circulation diseases, such as TTN, some respondents expressed that the pathways would differ from well babies that screened negative. One respondent asserted that babies with TTN frequently need admission to the neonatal unit to make the diagnosis securely.</td>
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<td></td>
<td>Another respondent stated that for the majority, however, they will be observed on postnatal ward.</td>
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<td></td>
<td>Regional variations may mean that ECG is unavailable, and an increased need to travel for investigations.</td>
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<td></td>
<td>For babies that screen positive, many respondents suggested it was reasonable to assume that a positive result, followed by investigation using the appropriate test (e.g. echocardiography for CHD, X-ray for pneumothorax) and clinical consultation, would identify the disease if present (i.e. 100% true positive rate).</td>
</tr>
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<td></td>
<td>The majority felt that false negative results would not have a detrimental impact on the subsequent diagnosis of the diseases of interest. However, it was noted that there is a lack of evidence to support this view.</td>
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<tr>
<td>Comparator</td>
<td>NIPE without universal PO but with diagnostic use.</td>
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<td>------------</td>
<td>-----------------------------------------------------</td>
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<tr>
<td>Outcome</td>
<td>Health outcomes for the newborn are the primary outcome of interest.</td>
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<td></td>
<td>Impact on parental anxiety and quality of life could be considered as an extension to a primary analysis.</td>
</tr>
<tr>
<td>Quantifying the potential benefit of PO screen</td>
<td>The group were not able to specify how much time is gained from screening, i.e. the benefit over conditions being detected through other routes.</td>
</tr>
<tr>
<td></td>
<td>The group were unable to refer to evidence that had examined the reduction in time to diagnosis of cCHD or any other condition associated with hypoxaemia.</td>
</tr>
<tr>
<td></td>
<td>The group agreed that conditions other than cCHD are very important, including: other CHD, sepsis, pneumonia, pneumothorax, TTN, transitional circulation, meconium aspiration, and PPHN.</td>
</tr>
<tr>
<td></td>
<td>It was not clear how detection from PO can be separated from other tests that may be given ante and post natal.</td>
</tr>
<tr>
<td></td>
<td>There may be value in having a screen test result to motivate further investigation rather than relying on clinical judgement alone, and that this value might vary with the experience and seniority of the staff member evaluating the newborn.</td>
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<tr>
<td></td>
<td>PO screening might pick up things that were missed due to errors in earlier testing and screening.</td>
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</tbody>
</table>
Model conceptualisation for newborn screening

The pathway by which universal PO screen might alter costs and outcomes for newborns with cCHD is reasonably well known and therefore formed the basis for our development of a proposed model structure. For newborns with cCHD there is evidence that morbidity and mortality increase when there is a delay in diagnosis and treatment [2]. Therefore, a delay in diagnosis can be described in terms of impacts on health-related quality of life and mortality, and in terms of health resources used to treat the consequences of delayed diagnosis of cCHD. Universal screening with PO can bring forward diagnostic investigation and hasten access to treatment in newborns who might otherwise have suffered significant health consequences. The difference in time to diagnosis occurs among those newborns who are undetected via symptoms, via antenatal screening, maternal risk factors, neonatal symptoms, and the existing NIPE prior to discharge. The health benefits are primarily among those newborns who, without screening, are discharged without detection of cCHD and who would be diagnosed symptomatically after experiencing serious complications. The set of tests to diagnose cCHD, associated stays in hospital, emergency visits, and procedures, in addition to the treatment for confirmed cCHD, determine the further resource use of those who leave hospital without a diagnosis. While the type of surgery received may be the same for patients diagnosed early versus those diagnosed at symptomatic diagnosis, earlier and planned treatment may be less costly compared to emergency presentation and treatment.

Figure 1 illustrates our understanding of the stages and potential pathways to diagnosis when screening newborns. To inform the cost-effectiveness model, we require the incidence of conditions for newborns eligible for a universal screen, excluding those diagnosed antenatally and symptomatically prior to NIPE and PO screening (Figure 1 elements a + b). The costs and health consequences of preventing symptomatic diagnosis are potentially greater for post-discharge presentation compared to pre-discharge presentation. This is because pre-discharge symptoms may be detected by healthcare workers and access to treatment is more immediate. Similarly, the reduction in time to diagnosis is likely to be greater for diagnoses converted from post-discharge symptomatic diagnosis compared to those converted from pre-discharge symptomatic diagnosis. To capture the benefit of PO screening, we need to identify how many additional newborns are diagnosed at screening (Figure 1 element c) that would otherwise have been diagnosed symptomatically after discharge (Figure 1 element f). We also need to identify how many additional newborns are diagnosed at screening (Figure 1 element c) that would otherwise have been diagnosed symptomatically before discharge (Figure 1 element d).
Neither the stakeholder feedback nor the literature review identified subgroups in which there are: (i) different baseline risk of pathologies associated with hypoxaemia and (ii) where the newborns in these subgroups would remain within a standard universal screen and care pathway in which we aim to evaluate the addition of routine PO. The ability to undertake sensitivity analyses to baseline risk of conditions was identified as an important functionality of any developed model that would be informative in combination with evidence as to the existence of any such subgroups.

The sensitivity and specificity of PO, as a test for cCHD, varies with time from delivery, with increased rates of false positives within 24 hours compared to after [51]. This indicates that costs and outcomes will be sensitive to the timing of the screen, and this impact may differ across diagnoses and subgroups. Given the stakeholder feedback on variation in the time at which PO may be administered, any model should be constructed to enable investigation of different times for screening and for receipt of treatment.

To include the range of diagnoses that are linked to hypoxaemia in the decision analytic model, we considered whether a pathway to changes in costs and/or outcomes could be identified and measured. The care pathway for newborns is complex and our stakeholder consultation indicated that it varied across units and birth settings. Any cost-effectiveness analysis should be structured to investigate sensitivity to the average cost of resources employed to follow up a screen positive result. To include other non-cardiac conditions that are linked to hypoxaemia in the decision analytic model (e.g. pneumonia and sepsis), we similarly considered what would be an identifiable pathway to changes in costs and/or outcomes given in Box 1. Supplementary Table A1 shows how we applied these criteria to hypoxaemia related diagnoses.
Box 1: Summary of criteria to permit inclusion of diagnoses in a screening model

A: Is there evidence of an increase in morbidity or mortality when there is a delay in diagnosis and treatment?
B: Would screening reduce the time to diagnosis and treatment?
C: Given the potential scale of any reduction in time to diagnosis, could this produce a clinically meaningful difference in outcomes?
D: Would screening alter other current screening methods or tests for babies with that diagnosis?
E: Are the impacts measurable and/or estimable within the timeframe of decision problem?

Evidence requirements and availability

Primary data collection in the area is complex and little is known about diagnosing conditions in the absence of PO screening. We summarise evidence to address the model requirements derived from our literature review and stakeholder consultation in Table 2.

Table 2: Evidence requirements for model

<table>
<thead>
<tr>
<th>Data item</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline risk of cCHD and other conditions</td>
<td>Rates for the general ‘well appearing’ babies born at term and for specific subgroups (maternal characteristics, including clinical history and presentation, socioeconomic deprivation and exposure to risk factors)</td>
</tr>
<tr>
<td>PO test performance</td>
<td>Performance for well appearing babies May also need to reflect differences in the way the PO is delivered in practice versus in experimental studies</td>
</tr>
<tr>
<td>Costs of adding PO screen to NIPE</td>
<td>Do not need to cost NIPE as this is apparent in the intervention and comparator arm</td>
</tr>
<tr>
<td>Time to diagnosis for comparator (NIPE only)</td>
<td>For cCHD and non-cCHD conditions (transitional circulation, sepsis, pneumonia, TTN, PPHN, RDS) Will reflect likely variation due to differences in clinical practice</td>
</tr>
<tr>
<td>Treatment effect for PO screen</td>
<td>Reduced time to diagnosis according to condition</td>
</tr>
<tr>
<td>Healthcare resource use associated positive screen</td>
<td>According to pathways specified by suspected condition – tests, procedures, additional time in hospital</td>
</tr>
<tr>
<td>Healthcare resource use associated with delayed diagnosis</td>
<td>For cCHD and non-cCHD conditions</td>
</tr>
<tr>
<td>Loss in QALYs for delayed diagnosis</td>
<td>For cCHD and non-CHD conditions</td>
</tr>
</tbody>
</table>

Estimating the reduction in time to diagnosis with PO screening represents the biggest challenge in populating the proposed model structure. First, the time to diagnosis with NIPE only must be
estimated, for each hypoxaemia-related diagnosis. Given the likely differences in neonatal testing and pathways of care, this information should be sought for the UK or in a setting likely to be generalisable to the UK. The PHE pilot study for PO only collected data on units that had implemented a screen strategy. Time to diagnosis was not the outcome of interest and so count data were collected. In the UK, the PHE pilot estimated that 50% - 60% of units have not implemented universal screening using PO. Routine data would seem an appropriate option to determine the time to diagnosis for NIPE, according to condition, and then also the treatment effect of PO screen in terms of reduced time to diagnosis.

4. Discussion

In this paper we have developed a conceptual model that could be used to determine the cost-effectiveness of using PO in the screening pathway for newborn babies and its impact on neonatal and infant care, engaging with experts throughout. Our literature review found that previous cost-effectiveness models of PO screening frequently failed to reflect the need for a generic measure of benefit to inform national screening decisions. They also only captured the impact of detection on CHD and more specifically cCHD. Our study shows how to broaden the value assessment to include diagnoses other than cCHD that have potential to alter the value of universal screening with PO. To our knowledge these efforts to understand PO screening in its entirety and for conditions other than cCHD have never been attempted.

We found that current evidence is not sufficient to populate a cost-effectiveness model of PO screening for hypoxaemia. Consultation with stakeholders confirmed that the benefit of PO is earlier diagnosis as a prerequisite for improving health outcomes. However, estimating the change in time to diagnosis from the introduction of PO screening represents the biggest challenge in populating a cost-effectiveness model. This is a common challenge in assessing the cost-effectiveness of screening tests [52].

As with all screening tests, the wider diagnostic and treatment landscape is highly impactful on the cost-effectiveness of PO, specifically related to antenatal screening programmes. The number of ‘well appearing’ babies with underlying conditions that could be identified by PO will diminish as antenatal screening improves, reducing the potential impact of PO screening. In general, any assessment of the cost-effectiveness of a screening programme should be mindful of changes in this landscape and consider relevant thresholds at which changes to other routes of diagnosis may impact the cost-effectiveness of the screening programme being evaluated.

Based on what we have learned from previous studies, the nature of the available evidence, and the stakeholder consultation we have outlined in this paper, we recommend that the next step for PO screening should be to conduct a threshold analysis seeking to determine the potential for it to be a cost-effective use of limited NHS resources, and the conditions under which this would occur. We recommend that modelling should include value of information analysis to estimate the value of additional evidence generation in the form of trial or routine data.
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