



Recommendation to the UK National Screening Committee (UK NSC) for population screening for critical congenital heart disease and significant non-cardiac conditions using pulse oximetry screening in addition to current routine screening

The FMCH reviewed the evidence and options presented and agreed the recommendation that pulse oximetry should not be introduced as an additional risk assessment to the routine screening programme.

A discussion paper presenting recent research on pulse oximetry (PO) and its value as an additional screening test was taken to the Fetal, Maternal, and Child Health (FMCH) reference group. The aim was to present and understand the research to date, and to agree recommendations on the use of pulse oximetry as a screening tool for consideration at the UK National Screening Committee (UK NSC).

In considering PO as an adjunct to routine practice the UK NSC has to fully understand the benefits and harms of the intervention on whole population-offered screening and with regards to the impact and implications of a positive screen result.

The recommendation is made against using pulse oximetry as a population based screening test because there is currently insufficient evidence to suggest that there is a greater benefit to babies than that afforded by the current screening programme, however there are harms associated with screening and the further investigations following a positive screen result.

It was acknowledged that a number of Trusts use pulse oximetry to some degree and that it would be helpful to have guidance for the use of PO in newborns on the basis of clinical judgment.

This paper reviews the research and evidence that went into the development of the recommendations taken to the FMCH.

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1 Introduction

The UK National Screening Committee (UK NSC) is seeking to understand the benefits and harms afforded by pulse oximetry (PO) in order to consider its potential value as an additional element to the current antenatal and newborn screening programmes.

Initial research sought to understand the potential of pulse oximetry to detect significant or life threatening congenital heart defects that might otherwise go unnoticed at an early stage in babies who appear to be well.¹

A number of papers including: an health technology assessment (HTA) funded primary study, cost effectiveness analyses, Cochrane review, and UK NSC review indicated that the identification of newborns with hypoxaemia using pulse oximetry will result in further investigations which lead to the identification of critical congenital heart defects (CCHD) or congenital heart defects (CHD). The research also showed that the investigations following a positive screening result also led the identification of other serious conditions, mainly respiratory infections and sepsis, which might also benefit from early identification at the pre-symptomatic stage.

The UK NSC needs to consider these additional findings to fully understand the extent of the benefits and harms to patients of using the technology. A discussion of pulse oximetry as an intervention to identify pre-symptomatic CCHD must also include the opportunity to identify other, non-symptomatic non-cardiac, conditions.

The 2016 pilot study² findings supported those of the 2014 review³ which presented evidence to demonstrate that pulse oximetry, as an extra stage in the clinical examination, increases the detection rate of critical or life-threatening CHDs at the newborn screening opportunity. However, the data are not robust enough to make clear decisions on the impact (harms and benefits) of the other non-cardiac findings. The data generated in the pilot study were used to inform additional analyses⁴ aimed at answering the questions posed relating to the identification of non-cardiac conditions following a positive PO screening result.

This paper brings together the key issues that have been identified in the research commissioned by the UK NSC over the last 3 years, to inform the current discussion and feed into recommendations relating to PO screening. A number of the documents referenced here are summarised in section 5 and have informed the recommendations to take this work forwards.

1 <https://www.evidence.nhs.uk/search?q=pulse+oximetry>

2 Evans C, Walker J, Ewer A, Cawsey M 'Newborn Pulse Oximetry Screening Pilot', May 2016 PHE Crown publications

3 Ewer AK, Furnston AT, Middleton LJ, Deeks JJ, Daniels JP, Pattison HM, et al. Pulse oximetry as a screening test for congenital heart defects in newborn infants: a test accuracy study with evaluation of acceptability and cost-effectiveness. *Health Technol Assess* 2012;16(2):v-xiii, 1-184. as cited in Knowles RL, Hunter RM, 'Screening for Congenital Heart Defects: External review against programme appraisal criteria for the UK NSC' (April 2014) University College London

4 The data in the pilot informed the subsequent research: statistical report; the workshop discussion; the cost effectiveness analysis

2.i Pulse Oximetry

Pulse oximetry is a quick, non-invasive test that measures the concentration of oxygen in the blood using a sensor applied to the hand or foot of a newborn. The test is ideally performed shortly after, and within 24 hours of, birth. Timing is important as the number of false positives is affected by when the test is undertaken. Low levels of oxygen, hypoxaemia, can indicate a heart problem, infection, or other health problem that requires further investigation.⁵

Should a newborn present with specific symptoms, for example: indicative of heart defect, respiratory illness, or sepsis, then they would be managed according to standard clinical guidelines, not as part of a screening opportunity to identify non-symptomatic conditions.

The consideration here is that pulse oximetry would be used in addition to the current screening regime to identify hypoxaemia in non-symptomatic babies, and generate further investigation for those babies with a positive result, thus enabling the identification of a condition that would benefit from earlier diagnosis.

PO screening was initially considered by the UK NSC for critical congenital heart defect (CCHD). Congenital Heart Disease (CHD) is one of the most common types of birth defect, affecting up to 8 in every 1,000 babies born in the UK. Around 1 in 200 babies has a heart problem that needs treatment. Critical or major congenital cardiac malformations are found in approximately 2 to 3 per 1,000 live births.⁶

Hypoxaemia can also be an indication of non-cardiac conditions and these should be considered as an additional outcome in any analysis exploring pulse oximetry as part of the routine screening.

In considering PO as a screening tool, the UK NSC has to fully understand the benefits and harms of the intervention on whole population-offered screening, not only for the identification of CCHD and CHD but with regards to the impact and implications of identifying the additional non-cardiac conditions as well.

2.ii Current antenatal and newborn screening

Routine screening provides opportunities for the identification of CHD both prenatally and postnatally. These occur as part of the fetal anomaly screening programme (FASP) which includes a series of ultrasound scans at different stages in the pregnancy, and, postnatally with the newborn and infant physical exam (NIPE), which comprises a newborn physical exam completed within 72 hours of birth and then again at 6 to 8 weeks of age.⁷

⁵ Knowles RL, Hunter RM, 'Screening for Congenital Heart Defects: External review against programme appraisal criteria for the UK NSC' (April 2014) University College London

⁶ <https://www.nhs.uk/conditions/pregnancy-and-baby/newborn-physical-exam/>

⁷ <https://www.gov.uk/government/publications/newborn-and-infant-physical-examination-programme-handbook/newborn-and-infant-physical-examination-screening-programme-handbook>

Less than half of all CHDs are detected prenatally⁸. The prevalence of congenital heart defects at live birth will depend on the extent of fetal detection and the proportion of fetal diagnoses resulting in termination of pregnancy. In a UK wide study of fetal diagnoses of serious CHDs in term infants, a fetal diagnosis was made in just under one quarter of affected pregnancies, approximately half of which ended in termination. Annually, around 100-150 pregnancy terminations in the UK are associated with CHDs.⁹

A range of tests performed as part of the current antenatal and newborn screening programme will result in a screen negative or screen positive result. Babies with screen positive clinical findings suggestive of CHD will be seen by a senior paediatrician with expertise in cardiology as required (urgency will depend on suspected condition).¹⁰

Often, serious CHDs are identified postnatally when an infant develops symptoms. However, early detection in the fetal or newborn period can enable the management of the condition at an earlier stage, and before symptoms present.¹¹

3 Recent research and analyses

The screening opportunities for CHD stated above are well established as part of the routine national screening offer. The UK NSC is reviewing the value of pulse oximetry (PO) screening as additional to the current newborn exam and in doing so has supported research to address the questions raised.

The research reviewed here includes:

- 'Newborn Pulse Oximetry Screening Pilot', (May 2016). Authors: Claire Evans, Jill Walker, Professor Andrew Ewer, Dr Matthew Cawsey;
- 'Comparison of admission rates to neonatal units between pulse oximetry screening and non pulse oximetry screening units – statistical report'. (6 July 2017), Authors: Sena Jawad, Chis Gale, Andrew Ewer;
- 'Summary of discussions following the Pulse oximetry screening workshop of 22 June 2018';
- 'Pulse oximetry as a screening test for critical congenital heart defects and other significant diagnoses in newborn infants – a cost effectiveness analysis' (February 2019) Authors: Tracy Roberts, Karen Pickering, Pelham Barton, Andrew Ewer

The initial pilot study¹² explored the feasibility of implementing pulse oximetry in Trusts and in doing so produced outcome data sets. These went on to inform the further analyses that explored outcomes for both CHD and sepsis and respiratory outcomes.

⁸ Knowles RL, Hunter RM, 'Screening for Congenital Heart Defects: External review against programme appraisal criteria for the UK NSC' (April 2014) University College London

⁹ ibid

¹⁰ <https://www.nhs.uk/conditions/pregnancy-and-baby/newborn-physical-exam/>

¹¹ Knowles RL, Hunter RM, 'Screening for Congenital Heart Defects: External review against programme appraisal criteria for the UK NSC' (April 2014) University College London

¹² Evans C, Walker J, Ewer A, Cawsey M 'Newborn Pulse Oximetry Screening Pilot', May 2016 PHE Crown publications

As the pilot study outcomes were used as a basis for the other analyses (as per the above list) and generated further discussion, it is necessary to understand how the data were generated and what information this provided.

The pilot study identified two sets of Trusts, chosen on willingness to participate, volume of births, access to level 3 neonatal care and paediatric cardiology, and geographical location. Set A) were Trusts already implementing pulse oximetry screening to some degree, and set B) Trusts, matched according to volume and neonatal unit level 3, which did not use pulse oximetry but would implement the technology as part of the study.

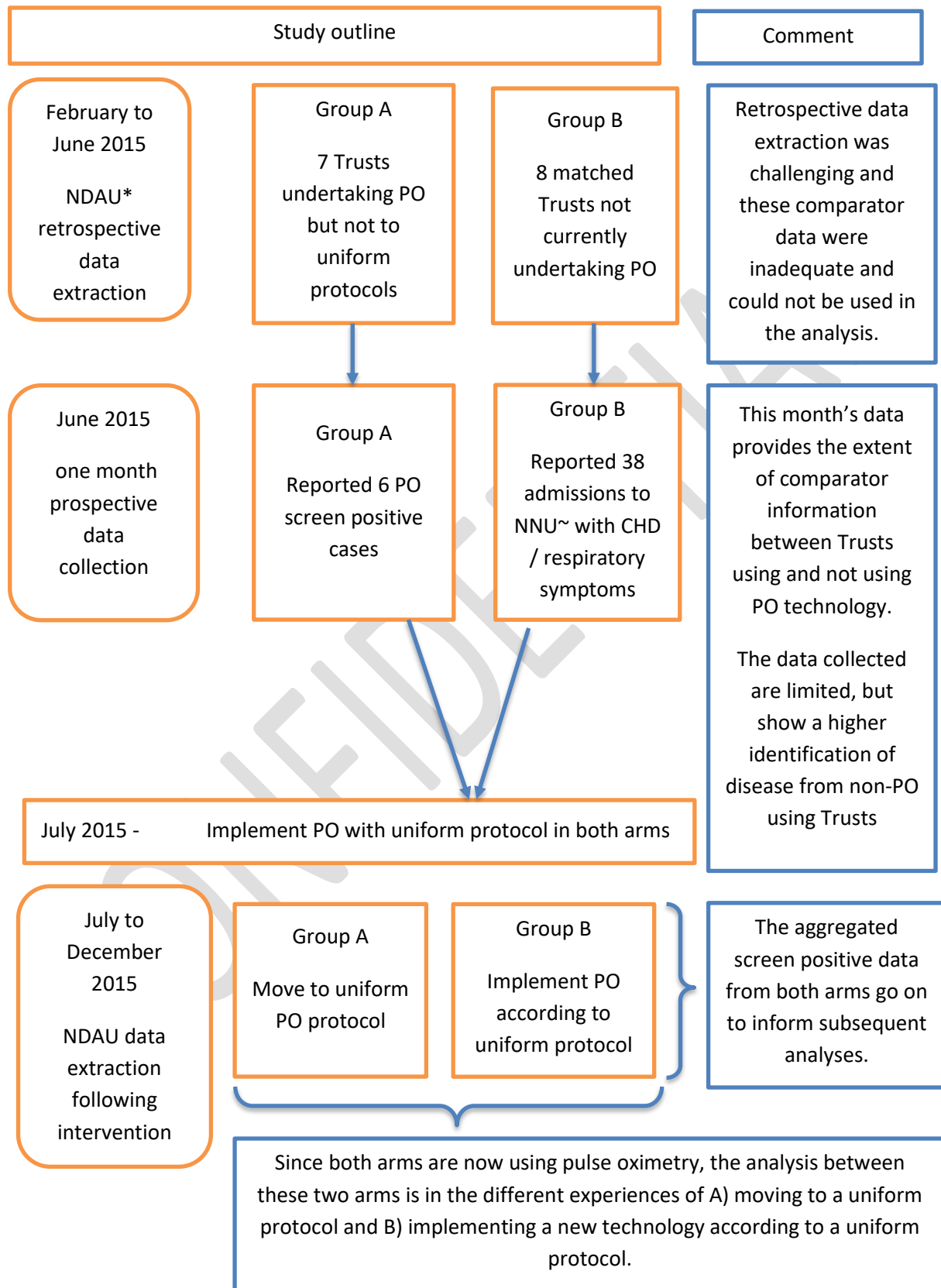
The pilot was conducted as:

- phase 1 (Feb 2015 to end May 2015) which established the study set up including baseline questionnaires and six months retrospective data collection from both arms of the study
- phase 2 (June 2015 to end December 2015), which progressed with one month data collection during usual practice in June 2015
- intervention implementation in July to end December 2015. This showed:
 - group A – moving from their usual PO screening practice to implementing a standardised protocol
 - group B – implementing PO screening as a new element, and using the standardised protocol as above.

Outcomes were collected at each stage, with varying degrees of success using the NIPE SMART IT system and from the associated NNUs from both arms.

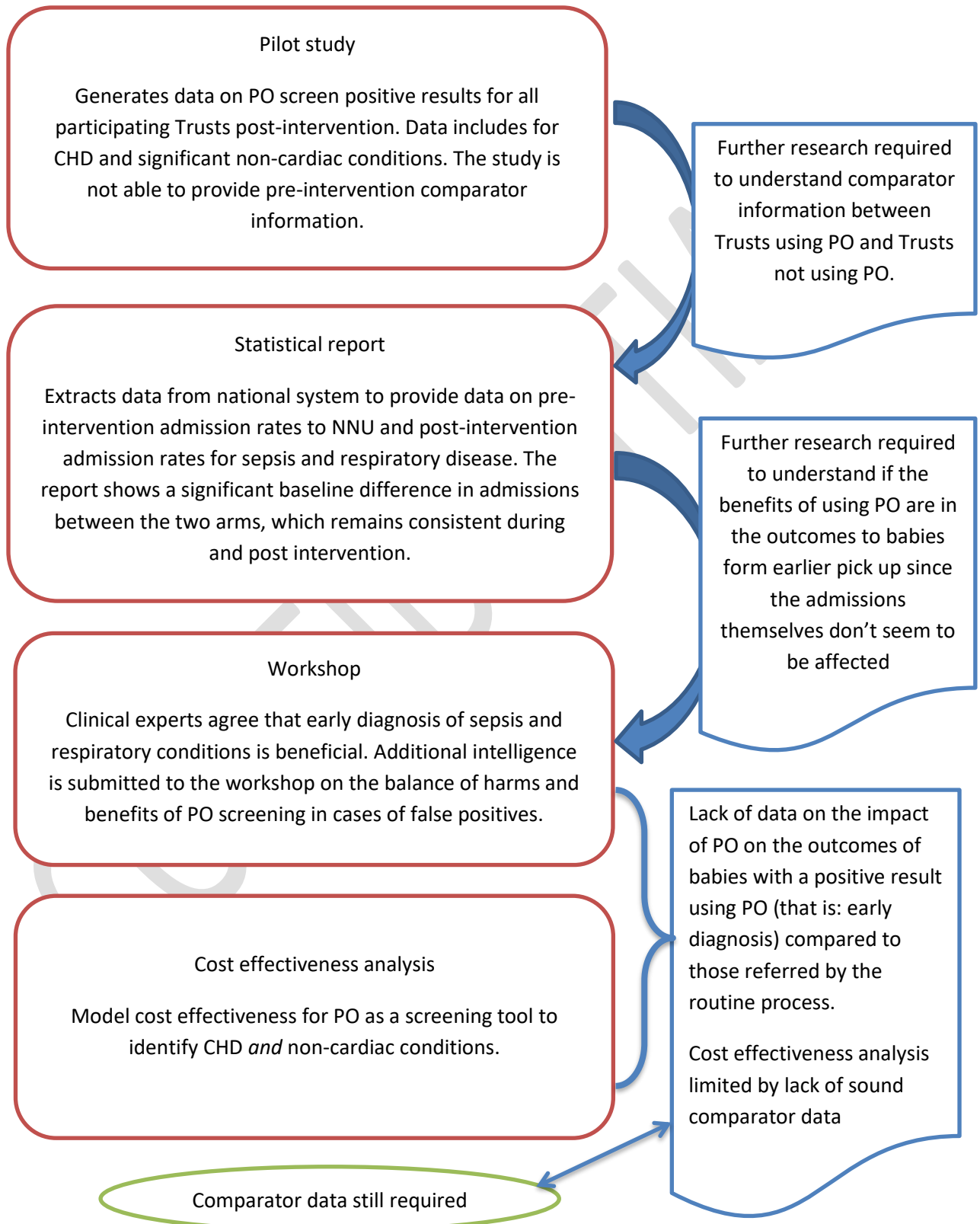
This is described with comment in figure 1 over the page.

Figure 1 The Newborn Pulse Oximetry Screening Pilot study process



*NDAU – neonatal data analysis unit
~NNU – neonatal unit

The pilot study generated a range of questions prompting further research, specifically with regards to comparator data, and a better understanding of the impact of PO on non-cardiac conditions. This is summarised in the diagram below with further detail of the additional research supplied in section 5.



4 Summary and options to inform recommendations.

That pulse oximetry screening identifies hypoxaemia which triggers further investigations and can lead to the identification of CHD and other significant non-cardiac conditions, is accepted.¹³

The research, analyses and workshop discussions undertaken over the last few years, as reflected here, to develop our understanding of the role of PO screening has also indicated that:

- Trusts find it challenging to implement PO according to a defined protocol
- it is challenging to identify comparable data sources: repeated efforts to develop, assume or use other data sources to provide the comparator have not been successful.
- PO screening does not appear to impact on neonatal unit (NNU) admissions.
- early identification of non-cardiac conditions will improve outcomes, but we do not have the outcome data to identify if PO screening leads to earlier admission and better outcomes.
- as screening criteria require a level of certainty that a programme would do more good than harm to *all* those offered the programme, the absence of outcome data for an un-screened comparator is a major (critical) impediment to decision making.
- advocates of screening in the UK and the US continue to assert that finding mildly hypoxic babies is worthwhile and the use of PO machines continues to rise.

The UK NSC is asked to consider pulse oximetry as an adjunct to routine screening, and the following options were considered by the FMCH reference group, to:

- Recommend against PO as an addition to the current screening programme.
- Implement PO as an additional test to the current screening programme.
- Propose further research to understand the degree to which the incidental findings are picked up differently or in a more timely fashion than through the NIPE or symptomatic presentation, and the outcomes for babies of this.
- Propose that the RCPCH/NICE (or other relevant guideline making body) develop guidance for the use of PO in newborns on the basis of clinical judgments, not as part of a routine screening programme for every baby.
- A combination of these options.

The FMCH agreed to recommend against introducing pulse oximetry as an addition to the routine screening programme.

The meeting discussed the need for comparator data and further evidence to support a future review. It was acknowledged that a number of Trusts use pulse oximetry to some degree and that it would be helpful to have guidance for the use of PO in newborns on the basis of clinical judgments.

¹³ *Newborn Pulse Oximetry Screening Pilot*, May 2016. *Health Technol Assess 2012*; as cited in Knowles RL, Hunter RM, 'Screening for Congenital Heart Defects: External review against programme appraisal criteria for the UK NSC' (April 2014) University College London

5 Recent research and analyses

The documents and reports reviewed are summarised below.

5.1 Newborn Pulse Oximetry Screening Pilot ¹⁴

The aims of the pilot were to:

- evaluate the feasibility of implementing newborn PO screening on NHS services
- establish the effect on clinical services when PO screening is undertaken as part of the newborn and infant physical examination NIPE.

The pilot study identified two arms comprising A) Trusts which were already using pulse oximetry and B) Trusts which were not using PO but which would implement the technology according to a defined protocol. The study process is described in the flow chart: figure 1. Page 6.

The phase one retrospective data collection between the two arms, which would provide comparator information, failed and the data could not be used. This means that the only comparator information available is from a single month (June) immediately prior to the intervention implementation in both arms. This is limited as only representing one month.

The admissions in the two arm in this month are also so different (3 screen positive vs 38 NNU referrals) they lead us to question the degree to which the two arms were adequately matched. This could be a function of only one month's data, however the subsequent report (5.2) using the same matched Trusts also shows a mis-match in baseline and outcomes.

The objectives as stated in the report ¹⁵were to:

- identify existing PO screening pathways already in use
- describe the variations in clinical workload, protocols and resources in Trusts already using PO screening
- describe the variations in Trusts which would implement PO screening as part of the study
- audit screening outcomes in all eligible babies (cardiac diagnoses and non-cardiac diagnoses in screen positive babies, referrals after a positive cardiovascular screen following NIPE or PO, deaths within 1 month of birth
- develop information to be used in the pilot
- support delivery of training for the pilot.

The project report of this pilot study was completed in May 2016 and fed back on the aims and objectives stated above.

With regards to these stated aims the pilot report suggests that: 'Overall the PO screening pilot appears to have achieved the main aims of demonstrating feasibility of screening

¹⁴ Evans C, Walker J, Ewer A, Cawsey M 'Newborn Pulse Oximetry Screening Pilot', May 2016 PHE Crown publications

¹⁵ pp14

without causing significant overload to clinical services.¹⁶ The limitations of the study suggest that this overall conclusion may not be so clear cut. There were issues associated with the adherence to the protocol: five of Group A Trusts and one Group B Trust failed to adhere to the protocol.¹⁷

Additional qualitative feedback suggests that using PO screening did not impact on the perceived admissions to NNU in 14 of the 15 Trusts but did in one Trust.¹⁸ However, this impact is reported by stakeholder questionnaire and does not reflect a quantitative assessment.

The data sets collected in phase one of the pilot to quantify referral variation between Trusts using and not using PO were inadequate to make comparisons between Trusts for this phase. The phase two data extracted provide information on outcomes following the implementation of pulse oximetry across both arms of the study. The outcomes are summarised in the report¹⁹

Test result data from the pilot

There seem to be some minor data transcription errors in this paper and CHD diagnoses are varying reflected as 13 or 14, and significant but non-cardiac diagnoses are reflected as 82 or 86 depending on which section is reviewed.²⁰ However this is minor and the report identifies the outcomes following 32,836 PO screens performed there were²¹:

- 239 babies with positive test results, of these:
- 8 had no diagnoses – unknown data
- 14 (or 13) had CHD diagnoses – true positives
- 135 were transitional circulation (healthy) – false positives
- 82 (or 86) had other significant but non-cardiac diagnoses – false positives but probably beneficial findings

The language of true and false positives for PO test positive babies, as reported in the pilot, can be understood differently if CCHD is identified as the target condition or if CCHD plus significant non-cardiac conditions as a whole is identified as the target condition. Thus any analysis needs to be clear as to what is being identified as true or false positive results. For example, this study refers to CCHD as the target condition thus the analysis considers all non CCHD conditions as false positives, that is: 239 positives of which 14 are true positives.

If one includes non-cardiac conditions in the screening target then of 239 positives there were 96 true positives (14 + 82).

16 Evans C, Walker J, Ewer A, Cawsey M 'Newborn Pulse Oximetry Screening Pilot', May 2016 PHE Crown publications pg 24

17 pg21

18 pg21

19 pg 106 – 111

20 pg106 /pg110

21 Pg 106

It is fundamental in implementing a national programme, where we potentially lead a non-symptomatic person through investigations and tests, to understand the harms and benefits of the screening intervention and to ensure that the benefits outweigh the harms.

The pilot study shows positive outcomes on the use of pulse oximetry for identifying CCHD, and the balance between the seriousness of this condition and harms associated with screening.

There is a lack of comparator data and the identification of the incidental findings of significant non-cardiac conditions raises further questions regarding the impact of pulse oximetry as a screening tool and the balance of benefits and harms.

Further research was agreed to better understand the full impact of pulse oximetry. The additional analyses used the data from the pilot study as a starting point to inform:

- The comparison of admission rates to neonatal units between pulse oximetry screening and non pulse oximetry screening units – statistical report (5.2 below)
- the pulse oximetry screening workshop of 22nd June 2018 (see 5.3 below), and
- the cost effectiveness analysis 'Pulse oximetry as a screening test for critical congenital heart defects and other significant diagnoses in newborn infants' (see 5.4 below),

5.2 Comparison of admission rates to neonatal units between pulse oximetry screening and non pulse oximetry screening units – statistical report.²²

The aim of this report is to determine the effect of introducing pulse oximetry screening on admission rates to neonatal units. The analysis explored if there was an increase or decrease in respiratory and sepsis admissions to neonatal units following the implementation of PO screening.

The data suggest that there is minimal or no increase in admissions following the introduction of PO screening.

This report focussed on the significant non-cardiac conditions, for which respiratory or sepsis admissions are used as the proxy measure. The data were taken from NNU admissions from the group A and group B Trusts identified in the pilot study. The data on admissions covers a greater time period than in the initial pilot report, but the Trusts are the same.

Table one, below, is taken from the report and summarised the admissions for both arms, during the study duration (which is longer than the pilot study) where July to December 2015 is the period of implementation of pulse oximetry according to uniform protocols in both groups of the pilot study.

²² Jawad S, Gale C, Ewer A 'Comparison of admission rates to neonatal units between pulse oximetry screening and non pulse oximetry screening units – statistical report'. (6 July 2017)

Table 1 Summary of bi-annual respiratory and sepsis admissions

	n respiratory and sepsis admissions / total admissions (%)					
	Jul – Dec 2014	Jan – Jun 2015	Jul – Dec 2015	Jan – Jun 2016	Jul – Dec 2016	All
Pulse Oximetry	2,346/3,922 (59.8%)	2,390/3,891 (61.4%)	2,612/4,237 (61.7%)	2,745/4,341 (63.2%)	2,968/4,784 (62.04%)	13,061/21,175 (61.7%)
Matched Controls	1,902/3,929 (48.4%)	2,001/3,906 (51.23%)	2,084/4,014 (51.9%)	2,131/4,101 (52.0%)	2,166/4,276 (50.7%)	10,284/20,226 (50.9%)

The row entitled ‘Pulse Oximetry’ can also be defined as the group A Trusts, and the ‘Matched Controls’ as group B Trusts in the pilot study. The matching was undertaken for the pilot study and included volume and throughput, geographical location and access to level 3 NNU.

The first two columns covering July 2014 to June 2015 reflects the admissions from two arms where A is using pulse oximetry as an adjunct to routine screening and B is using only routine screening. These two columns generate a question regarding the matched nature of the two arms, since the proportion of admissions at this baseline is so different: with 11.4% more admissions in group A than group B. This variance is maintained throughout the study (between 9.8% and 11.34%) including at the point of full PO implementation across both arms.

July to December 2015 covers the period of the pilot study, when group A Trusts started to apply a uniform protocol to using pulse oximetry and group B Trusts started to implement pulse oximetry.

The final two columns cover January to December 2016. It is not clear whether group B Trusts stopped using pulse oximetry at this point as this was after the pilot. It is also not clear the degree to which any Trust continuing to use PO did so according to a uniform protocol.

The data only reflect admissions to the NNU which attempts to answer the question of comparison between the two arms. Any assumptions or data cleansing are not described, but using the data presented there appear to be no particular increases in admissions to NNU following the implementation of pulse oximetry, or the streamlining of protocols.

If we assume that the two arms are suitably matched (whether they are is beyond the scope of this review, and at this point may not matter), both show little difference in the rate of admissions for the two outcomes. There is no significant increase in admissions to NNU from sepsis and respiratory conditions following the introduction of PO screening.

The outcome that admissions are relatively consistent with or without PO screening leads us to the next question: Are the outcomes for those babies admitted to NNU better as a result of potentially earlier pick up from PO screening. Thus we need to understand if the admission is in fact earlier, and what the outcomes are for babies in the two arms of the study.

The workshop summarised below was set up to consider the question of harms and benefits of earlier identification and management of the conditions for which hypoxaemia might be indicative.

5.3 Summary of discussions following the Pulse oximetry screening workshop of 22 June 2018

A record of the discussion of the workshop of 22nd June 2018 was reviewed.

The purpose of the workshop was:

- to note that pulse oximetry will identify hypoxaemia which is indicated for CCHD and other, non-cardiac, conditions, and
- to consider the outcomes for these other conditions, with regards to harms and benefits of early identification in PO screened or in unscreened populations.

The workshop was set up by the UK NSC Secretariat, chaired by Graham Shortland to develop an expert clinical view on the net effect to babies and their families of a screen positive result.

The pilot data identified that of 239 babies testing positive with PO screening, 82 (or 86) patients did not have CHD but did have a significant other non-cardiac condition and 135 babies were in fact healthy. All of these screen positive babies had further investigations.

The workshop explored the implications resulting from positive test results for healthy babies, and babies with significant other non-cardiac conditions. The group considered the benefits of earlier diagnosis and potential harms of over-diagnosis and follow up of false positives.

The group were clear that for 6 of the 8 additional conditions there would be some clinical benefit to earlier diagnosis, in one condition (pneumothorax) no clinical benefit and in one condition (culture negative sepsis) there are some harms and some benefits. For the healthy babies, there is some harm from unnecessary investigations and delayed discharge.

Additional research²³ and discussions at this workshop suggest that the harms described (delayed discharge, worry from false positives) are likely to be broadly acceptable to parents, and are balanced by the potentially serious nature of a late identification of the incidental conditions.

The clinical judgement of benefit from earlier diagnosis is not disputed, however, it is unclear from the pilot study whether pulse oximetry impacts on these outcomes for the following reasons:

- The protocols for using pulse oximetry were not fully adhered so we do not have adequate timings data to fully understand the early nature of the referral outcomes.
- We do not have data on the timings or outcomes of the NIP exam.

²³ Ewer – presentation at workshop on harms and benefits

- The statistical report showed no apparent difference in admissions to NNU for respiratory and sepsis (5.2), but provided no health outcomes data.

In order to include early diagnosis of other conditions in a rationale for implementing PO screening as an adjunct to routine practice we will need to explore further the outcomes of babies with a positive PO screening result, compared to outcomes in routine practice.

5.4 Pulse oximetry as a screening test for critical congenital heart defects and other significant diagnoses in newborn infants – a cost effectiveness analysis²⁴

The aim of this study was to provide a cost effectiveness analysis for pulse oximetry screening test as an adjunct to the NIPE for CCHD *and* other significant conditions in newborn infants versus the clinical exam alone. The analysis was based on cost and timely diagnosis (i.e.: before discharge).

A cost-consequence analysis and decision-analytic model was constructed using a number of assumptions, informed by data from other sources and expert opinion. The cost effectiveness-analysis was based on an outcome of timely diagnosis.

The assumptions from two different data sets to complete two different pathways in the model led to two different implied prevalence rates for CCHD and other significant diagnosis. Consequently two separate analyses were attempted to estimate a range for the cost effectiveness ratio and different scenarios in terms of unnecessary tests experienced by infants as a result of Pulse Oximetry screening. Incremental cost-effectiveness ratios (ICERs) in terms of cost per case of timely diagnosis were estimated.

Unfortunately after much work and discussion, the results of the analyses are considered unsound. This is because there is no nationally accepted prevalence for the target condition of CCHD and other significant diagnosis with which to calibrate the many assumptions.

It is concluded that more complete data are need for further analysis and research should include a true non-screened comparator with infants followed up. Future studies should also include qualitative information from parents about their concerns regarding unnecessary invasive tests.

²⁴ Roberts T, Pickering K, Barton P, Ewer A 'Pulse oximetry as a screening test for critical congenital heart defects and other significant diagnoses in newborn infants – a cost effectiveness analysis' (February 2019)