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| <b>Institution:</b> University of Birmingham   |   |   |
| <b>Unit of Assessment:</b> UoA 1, Clinical Medicine  |   |   |
| <b>Title of case study:</b> Reducing death from critical congenital heart defects in newborn babies using pulse oximetry screening   |   |   |
| <b>Period when the underpinning research was undertaken:</b> 2006–2020   |   |   |
| <b>Details of staff conducting the underpinning research from the submitting unit:</b>   |   |   |
| <b>Name(s):</b><br><br>Andrew K. Ewer<br>Jon Deeks<br>Tracy Roberts  | <b>Role(s) (e.g. job title):</b><br><br>Professor of Neonatal Medicine<br>Professor of Biostatistics<br>Professor of Health Economics | <b>Period(s) employed by submitting HEI:</b><br><br>1996 to present<br>2006 to present<br>1998 to present |
| <b>Period when the claimed impact occurred:</b> August 2013–December 2020  |   |   |
| <p><b>Is this case study continued from a case study submitted in 2014?</b> Yes</p> <p>“Pulse oximetry screening to detect heart disease in newborn babies” was submitted as an Impact Case study for REF 2014. This case greatly extends that work and is supported by new research and demonstrates a broad range of novel impacts. New research includes an influential Cochrane review [R5], the identification of non-cardiac conditions and algorithm improvements [R4, R6]. New impact is extensive, led directly by Ewer and colleagues, and underpinned in part by new research.</p>  |   |   |
| <p><b>1. Summary of the impact</b></p> <p>Research from the University of Birmingham has significantly <b>reduced deaths in newborn babies suffering from critical congenital heart defects (CCHD)</b> through the implementation of pulse oximetry screening (POS) as a diagnostic tool. CCHDs are a major cause of death and serious morbidity in newborn babies yet previous screening methods missed up to 50% of cases. In contrast POS, a simple, safe and cost-effective test, increases identification of babies with CCHD to up to 92%. As a consequence, patient outcomes have been improved as introduction of POS reduces mortality from CCHD by over 33% and also identifies babies with other potentially serious non-cardiac conditions. This has been achieved through <b>changing guidelines and health policy to recommend POS across five continents, leading to widespread changes in clinical practice.</b></p>   |   |   |
| <p><b>2. Underpinning research</b></p> <p>Congenital heart defects (present at birth) are a leading cause of infant mortality in developed countries, accounting for 40% of deaths from congenital malformations, with most occurring in the first month of life. “Critical” congenital heart defects (CCHD) are most likely to cause death and occur in around 2/1000 babies. Affecting up to 1,600 babies a year in the UK alone, less than 50% of CCHD are detected antenatally (before birth) and up to 45% of the remainder of babies will present with death or acute collapse before diagnosis. Although surgery greatly improves survival, poor condition at presentation worsens surgical outcome, and there is a higher risk of life-long neurodevelopmental impairment making early detection an urgent priority.</p> <p>Blood oxygen levels are frequently low in CCHD and can be detected using pulse oximetry, a non-invasive method of measuring oxygen levels. Pulse oximetry’s role in <i>screening</i> for CCHD, initially explored in the early 2000s, produced inconclusive results. In 2007, Andrew Ewer, Professor of Neonatal Medicine and a team from the University of Birmingham (UoB) conducted the first systematic review (a robust summary of all available research) of pulse oximetry screening (POS) identifying encouraging results but highlighting a lack of sufficient evidence of test accuracy to recommend it in routine practice. Larger, more robust studies to confirm the accuracy, acceptability and cost-effectiveness of POS were therefore recommended (Thangaratinam <i>et al</i> Arch Dis Child Fetal Neonatal 2007;92:F176-80).</p> |   |   |

In 2007, the National Institute for Health Research funded the multi-centre PulseOx study (HTA, 2007–2010), led by Ewer and run by the Birmingham Clinical Trials Unit. This study assessed the test accuracy of POS for detecting CCHDs in newborns. It was the largest UK study in this field, screening 20,055 newborn babies, and the first to assess the added value of POS in modern healthcare systems where antenatal ultrasound screening was widely available. The study used robust methodology to **generate precise estimates of the test accuracy** [Prof. J. Deeks, R1], **cost-effectiveness** [Prof. T. Roberts R2] **and acceptability of pulse oximetry and the value added to existing screening** [R2]. This study demonstrated that adding POS to existing screening tests resulted in 92% of CCHDs being detected before discharge and confirmed POS to be a **safe, feasible, acceptable and cost-effective screening test for CCHD** [KF1]. The results significantly enhanced available evidence indicating that POS could be introduced as a routine procedure. In 2012, Ewer led a second systematic review (published in the Lancet and including over 230,000 screened babies) **that concluded that POS met the criteria for routine screening [of CCHD] set by International Screening Guidelines** [KF2; R3].

Since 2014, Ewer's team have published **additional research** describing outcomes of routine POS screening in UK clinical practice [R4] **which confirm R2's findings in a much larger real-world setting and also clearly identify the additional benefits of POS in detecting non-cardiac conditions (such as breathing problems and infections)** [KF3; R4]. The team published a third systematic review for the Cochrane library [R5] **involving over 450,000 screened patients** which confirmed, with remarkable consistency, the finding of their previous review [R3; KF2].

In a further evidence synthesis, the relative advantages and disadvantages of different potential screening algorithms were evaluated and clear recommendations were made regarding optimum timing of screening and threshold values for a positive test [R6; KF4].

### Key Findings

**KF1.** POS is a safe, feasible, acceptable cost-effective test which will increase identification of CCHD to 92%.

**KF2.** POS meets the criteria for universal screening for CCHD.

**KF3.** POS will also identify important non-cardiac conditions (such as infections) while babies are still asymptomatic.

**KF4.** Modification of the POS screening algorithm will identify a greater proportion of infants with conditions of interest (i.e. CCHD and other non-cardiac problems).

### 3. References to the research

**R1.** Ewer AK, Middleton LJ, Furmston AT, Bhojar A, Daniels JP, Thangaratinam S et al. Pulse oximetry as a screening test for congenital heart defects in newborn infants (PulseOx): a test accuracy study. Lancet 2011; 378(9793): 785-94. Epub 2011 Aug 4. DOI: **10.1016/S0140-6736(11)60753-8**

**R2.** Ewer AK, Furmston 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):1-184. DOI: **10.3310/hta16020**

**R3.** Thangaratinam S, Brown K, Zamora J, Khan KS, Ewer AK. Pulse oximetry screening for critical congenital heart defects (CCHD) in asymptomatic newborns: A systematic review and meta-analysis involving 229 421 babies. Lancet 2012 ; 379 (9835): 2459-2464 DOI: **10.1016/S0140-6736(12)60107-X**

**R4.** Singh AS, Rasiah SV, Ewer AK. The impact of routine pre-discharge pulse oximetry screening in a regional neonatal unit. Arch Dis Child Fetal and Neonatal Ed 2014; 99:F297-F302. Published Online First: 19 March 2014 DOI:**10.1136/archdischild-2013-305657**.

**R5.** Plana MN, Zamora J, Suresh G, Fernandez-Pineda L, Thangaratinam S, Ewer AK. Pulse oximetry screening for critical congenital heart defects. Cochrane Database of Systematic Reviews 2018, Issue 2. Art. No.: CD011912. DOI: 10.1002/14651858.CD011912.pub2.

**R6.** Ewer AK, Martin GR. Newborn pulse oximetry screening: which algorithm is best? Pediatrics 2016;138:e20161206. DOI: 10.1542/peds.2016-1206

#### 4. Details of the impact

The impact underpinned by the research is **improved outcomes for newborn babies** as a result of the global uptake of pulse oximetry screening, brought about through the widespread introduction of national guidelines, and the transformation of clinical practice.

##### 1. Improved outcomes for newborn babies by increasing early detection of, and reducing death from, CCHD

The implementation of Pulse Oximetry Screening (POS) **increases the identification of babies with CCHD to up to 92%**. This is a dramatic change as previous screening methods missed up to 50% of affected babies. The impact on neonatal death (mortality) and early identification of babies with potentially life-threatening conditions as a result of implementing POS is demonstrated by the following evidence:

- In the **USA**, in 2017, evidence from over 27 million births showed that the implementation of POS reduced neonatal mortality from CCHD by over 33% and reduced deaths from other cardiac causes by 21% leading to 120 lives saved per year in the USA alone [S1]. Those babies who are picked up before acute collapse also benefit from better surgical outcomes and reduced postoperative complications.
- In the **UK**, evidence from Birmingham [R4] showed that routine screening consistently detects one previously unidentified case of CCHD for every 2,873 screens performed. POS also detects many babies (up to 79% of babies with a positive test but no heart problem) with other non-cardiac conditions (such as breathing problems and early-onset infection (sepsis)) which may also be potentially life-threatening. These were detected at a rate of one non-cardiac condition for every 156 screens performed. [R4]
- In **China**, over 2.5 million babies have been screened and over 13,000 cases of CCHD detected (2019) [S2i].

##### 2. Introduction of guidelines and health policy internationally to mandate routine POS

In this impact period, Ewer has **directly informed the introduction of national clinical guidelines and health policy across five continents**, including a Europe-wide consensus statement led by Ewer [S3]. Ewer has also advised clinicians and health officials in Australia, China, France, Germany, Israel, Kuwait, Netherlands, New Zealand, Poland, Saudi Arabia, 18 South and Central American countries (SIBEN), Spain and Sri Lanka in addition to working closely with the NSC in the UK [S4i]. As a result, the following countries have made **changes to guidance or national policy** in order to enhance the early detection of CCHD in newborns:

- Austria (2014) [S5i], Canada (2017) [S5ii], Germany (2017) [S5iii], Nordic countries (2014) [S5iv], Spain (2017) [S5v] and SIBEN (2016) [S5vi] have introduced national clinical recommendations to implement universal POS for newborn babies.
- China (2018) [S2i], Israel (2019) [S2iv], New Zealand (2020) [S5vii], Saudi Arabia (2016) [S5viii] and Sri Lanka (2017) [S5ix] have introduced national policies to require routine pre-discharge POS.

All recommendations and policies reference Ewer's research extensively and clearly attest to the importance of his work as influencing the change. That these changes were a direct result of Ewer's work is confirmed in the following statements [S2 i–viii]:

- The Principal Advisor to the Chinese Government on POS stated '[...] evidence developed by [Ewer's] team was fundamental in prompting [...] China to consider adoption of [POS]' [S2i].
- The Spanish National guideline coordinator stated 'the scientific work of [Ewer ...] heavily influenced the decision [...]' [S2ii] and the Spanish guideline lead stated 'With [Ewer's] work, it has been possible to develop a European consensus that has served as a guide for most of the European scientific societies.' [S2iii]
- The Israeli Neonatal Society stated '[Ewer's] impressive work and experience, [...] convince[d] our professional society of neonatology to consider introducing [...] routine screening' [S2iv].
- The Director of Hospital Affairs, Saudi Arabian Ministry of Health stated '[Ewer's] contribution in establishing the national [POS] protocol played a significant role.' [S2v]
- The senior clinical lead for New Zealand's POS workgroup stated 'The substantial and broad work of [Ewer ...] had a major impact on the work of the [NZPOS] Committee and the National Screening Advisory Committee of [NZ] Ministry of Health' [S2vi].
- The General Director of SIBEN acknowledged Ewer as 'the leader and expert opinion of SIBEN's [POS] consensus [...] across 18 Ibero-American countries'. [S2vii]

In this impact period, POS testing has become universal in the USA (2018); that Ewer directly led to this change is confirmed by the lead author of the USA POS recommendation, who stated that Ewer's work was 'central to informing the evidence review process' and 'the data he continues to collect [R6; S6] are central to ongoing screening recommendations' [S2viii].

### 3. Widespread changes to clinical practice implementing POS in the UK and other countries

Ewer's work **has influenced clinical practice leading to an improved uptake of POS within UK maternity units and improved access to screening for newborn babies.** This is evidenced by a survey published in the Lancet that shows that 51% of UK maternity units were utilising POS in 2020 — a significant increase from 18% in 2012 [S7]. In 2015, the National Screening Committee (NSC) instigated a POS pilot study (with Ewer as the clinical advisor) [S4i] and a public consultation on POS in 2019 [S4ii]. The response to the consultation was substantial, with 173 submissions, 85% of which were supportive of POS including support from Royal College of Paediatrics, British Association of Perinatal Medicine, UK Neonatal Society, British Congenital Cardiac Association and Congenital Cardiac Nurses Association. Support also came from five charities and 69 parents [S4ii].

**UK clinical practice has been further changed through the lobbying of charities and the public.** UK charity Tiny Tickers have directly and concretely changed practice by donating 188 pulse oximeters to UK maternity units between 2017 and November 2020. The Chief Executive of the charity stated '[Ewer's] ground-breaking research into PO screening is having a significant impact for babies not just in the UK, but around the world [...] hundreds of thousands of babies each year are now able to access the test that could help save their lives by spotting their CHD [...]' [S8i] Ewer has further worked with the Children's Heart Federation, Little Hearts Matter, Children's Heartbeat Trust and Tiny Tickers on targeted awareness campaigns to raise public awareness about PO screening [S4ii: pp. 34, 56, 147, 161] so that parents are empowered to lobby for practice change [S4ii].

Ewer has sought to **further increase uptake in clinical practice** in the UK, through a series of presentations and webinars in the eight UK regional neonatal networks [NN] where uptake is less than 50% [S9i–ii]. This is proving effective, and the clinical lead for South West NN stated Ewer's work 'provided substantial evidence' and the webinar 'galvanised substantial support' for POS which 'directly led to multiple units across the SW [NN] undertaking detailed work towards implementation' [S9(iii)]. The national Neonatal Network lead for Scotland stated that 'An output of [Ewer's] webinar has been to convene a National working group to consider wider implementation of routine pulse oximetry screening across Scotland' [S9iii].

Beyond the UK, working to **enhance disease awareness and prevention in low-income countries**, Ewer acts as an advisor to the US Newborn Foundation's BORN project in 12 countries (including rural China, Mongolia, Mexico, Pakistan and six African countries) helping them explore the opportunities of using PO as a screening method for other conditions which lead to low oxygen levels in newborn babies such as pneumonia [R4]. The impact of his work is clearly evidenced in a statement from the co-chair of the Board of the Newborn Foundation who said 'I can say with confidence that our foundation and research partners have been able to impact global health policies in 6 countries and counting, in part due to [Ewer's] steadfast willingness to share his knowledge and expertise.' [S8ii]

## 5. Sources to corroborate the impact

**S1.** Abouk R, Grosse SD, Ailes EC, Oster ME. Association of US State implementation of newborn screening policies for critical congenital heart disease with early infant cardiac deaths. *JAMA*. 2017;318(21):2111-2118. DOI:10.1001/jama.2017.17627

**S2.** Collation of statements of evidence of impact from international KOLs in public health, neonatology and cardiology across (i) China, (ii-iii) Spain, (iv) Israel (v) Saudi Arabia, (vi) New Zealand (vii) Latin America and (viii) USA. (2019).

**S3.** Manzoni P, Martin GR, Sanchez Luna M, Mestrovic J, Simeoni U, Zimmermann L JI, Ewer AK. Pulse oximetry screening for critical congenital heart defects: a European consensus statement. *Lancet Child and Adolescent Health* 2017;1:88-90. Published Online August 30, 2017, DOI:10.1016/S2352-4642(17)30066-4.

**S4.** (i) [POS pilot study](#) and (ii) Weblink to [Public consultation responses](#)

**S5.** Collation of National recommendations and policies for pulse oximetry screening including (i) Austria (2014), (ii) Canada (2017), (iii) Germany (2017), (iv) Nordic countries (2014), (v) Spain (2017) (vi) SIBEN (2016), (vii) New Zealand (2020), (viii) Saudi Arabia (2016) and (ix) Sri Lanka (2017).

**S6.** Martin GR, Ewer AK, Gaviglio A, Hom LA, Saarinen A, Sontag M, Burns KM, Kemper AR and Oster ME. Updated Strategies for Pulse Oximetry Screening for Critical Congenital Heart Disease. *Pediatrics* 2020;146:e20191650; DOI: 10.1542/peds.2019-1650

**S7.** Brown S, Liyanage S, Mikrou P, Singh A, Ewer AK. Newborn pulse oximetry screening in the UK: a survey of practice in 2020. *Lancet* 2020;396:881. DOI:10.1016/S0140-6736(20)31959-0.

**S8.** Collation of testimonials from Children's Heart charities (i) Tiny Tickers, (ii) Newborn Foundation.

**S9.** Collation of (i) Meeting agenda, (ii) Webinars and (iii) supporting testimonials from UK Neonatal Network leads, illustrating impact on Neonatal Networks across the UK.