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# Neonatal encephalopathy: a systematic review of reported treatment outcomes

Fiona Quirke ,[1,2,3] Linda Biesty,[4,5] Malcolm Battin ,[6] Frank Harry Bloomfield ,[7] Mandy Daly ,[8] Elaine Finucane,[5] Patricia Healy,[4] Tim Hurley,[1] Jamie J Kirkham ,[9] Eleanor Molloy,[10,11] David M Haas,[12] Shireen Meher,[13] Elaine Ní Bhraonáin,[14] Karen Walker ,[15,16] James Webbe ,[17] Declan Devane[2,5]

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For numbered affiliations see end of article.

**Correspondence to**
Fiona Quirke; 22306056@studentmail.ul.ie

## ABSTRACT

**Background** Neonatal encephalopathy (NE) is a multi-organ condition potentially leading to death or long-term neurodisability. Therapeutic hypothermia is the standard treatment for NE; however, long-term impairments remain common. Studies of new treatments for NE often measure and report different outcomes. Core outcome sets (COSs), a minimum set of outcomes to be measured and reported in all studies for a condition, address this problem. This paper aimed to identify outcomes reported (primary, secondary, adverse events and other reported outcomes) in (1) randomised trials and (2) systematic reviews of randomised trials of interventions for the treatment of NE in the process of developing a COS for interventions for the treatment of NE.

**Methods** We completed a systematic search for outcomes used to evaluate treatments for NE using MEDLINE, Embase, Cochrane CENTRAL, the Cochrane Database of Systematic Reviews and the WHO International Clinical Trials Registry Platform. Two reviewers screened all included articles independently. Outcomes were extracted verbatim, similar outcomes were grouped and outcome domains were developed.

**Results** 386 outcomes were reported in 116 papers, from 85 studies. Outcomes were categorised into 18 domains. No outcome was reported by all studies, a single study reported 11 outcomes and it was not explicitly stated that outcomes had input from parents.

**Discussion** Heterogeneity in reported outcomes means that synthesis of studies evaluating new treatments for NE remains difficult. A COS, that includes parental/family input, is needed to ensure consistency in measuring and reporting outcomes, and to enable comparison of randomised trials.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There are numerous randomised trials and systematic reviews of randomised trials for interventions for treating neonatal encephalopathy.

### WHAT THIS STUDY ADDS

⇒ We have identified 66 unique outcomes from 85 studies. Previously, a systematic review identifying the outcomes reported in randomised trials and systematic reviews of randomised trials of interventions for treating neonatal encephalopathy did not exist.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Identifying the heterogeneity in outcomes reported will help inform the development of a core outcome set to help standardise the outcomes measured and reported in future studies.

## INTRODUCTION

Neonatal encephalopathy (NE) is a neurological syndrome that can occur in late preterm and term infants.[1] Consequences of NE may include the development of cerebral palsy, seizure disorders, cognitive impairments, developmental impairments, multi-organ dysfunction and death.[2 3] The causes of NE can vary, including hypoxic-ischaemic injury (resulting in hypoxic-ischaemic encephalopathy), metabolic disorders, neonatal stroke, infection, maternal risk factors, placental complications and other genetic and epigenetic factors.[4] It is estimated that the incidence of NE is between 3 and 8.5 per 1000 live births.[5 6]

A systematic review of 11 randomised controlled trials of therapeutic hypothermia in late preterm and term neonates with moderate-to-severe encephalopathy found that this therapy reduces the risk of death and neurodevelopmental disability by 25%.[7] Therapeutic hypothermia is the standard treatment for moderate-to-severe NE in many countries in the developed world.[8 9] However, evidence for the efficacy of therapeutic hypothermia is limited to a narrow therapeutic window of 6 hours from birth[10] requiring an early diagnosis. Furthermore, long-term neurodevelopmental impairment still occurs in many survivors with moderate-to-severe encephalopathy treated with therapeutic hypothermia[7] resulting in the development of novel neuroprotective treatment strategies. Recent clinical trials of other treatments

include erythropoietin and darbepoetin,[11–17] magnesium sulfate,[18] 2-iminobiotin[19] and xenon gas.[20]

There are an increasing number of clinical trials of treatments for NE. Yet, a significant challenge arises in comparing the effectiveness of different interventions from different studies. Many studies measure and report different outcomes to determine the effectiveness of treatments. The lack of standardisation of outcomes measured means that researchers conducting evidence synthesis in reviews and meta-analyses cannot compare interventions and truly determine if a new intervention is better than the standard treatment or not.

To overcome this, the Core Outcome Measures in Effectiveness Trials (COMET) initiative recommends developing a standardised set of outcomes, known as a core outcome set (COS). A COS is an agreed, standardised set of outcomes that should be measured as a minimum in all studies for a health condition.[21] This allows researchers to compare the outcomes reported in the results of trials. Although researchers may measure other outcomes relevant to their trial, the COS should always be measured and reported. Developing a COS involves presenting key stakeholders with the outcomes commonly measured, typically identified by a systematic review, and asking them to prioritise the most critical outcomes using consensus techniques.

The objective of this paper was to identify outcomes reported (primary, secondary, adverse events and other reported outcomes) in (1) randomised trials and (2) systematic reviews of randomised trials of interventions for the treatment of NE as the initial step in the development of a COS for interventions for the treatment of NE.

## METHODS

The study consisted of a systematic review of completed randomised trials and systematic reviews of randomised trials of interventions for the treatment of NE. The literature search was conducted in December 2019 and WHO registry trials were added in April 2020. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[22] and COMET[21] guidelines are used to report the conduct and findings of this review.

### Protocol and registration

The protocol was registered with the PROSPERO database (CRD42020170265) and is contained within the protocol 'COHESION: Core Outcomes in Neonatal Encephalopathy (Protocol)'.[23]

### Eligibility criteria

The criteria for eligible studies were developed using the PICOS method (Population, Intervention, Comparator, Outcome and Study Design):

#### Population

Infants diagnosed and treated for NE, hypoxic-ischaemic or perinatal asphyxia/birth asphyxia encephalopathy; infants greater than or equal to 35 weeks' gestation. Where mixed gestational age of at least 80% of infants must be greater than or equal to 35 weeks' gestation.

#### Intervention

Any intervention for treating NE, hypoxic-ischaemic encephalopathy or perinatal/birth asphyxia.

#### Control/comparator

Comparing any intervention for the treatment of NE/hypoxic-ischaemic encephalopathy, or perinatal asphyxia with another treatment, placebo, standard care or nothing.

#### Outcome

All outcomes (related to the effect of the intervention) were included.

#### Study design

Randomised trials (last 20 years); systematic reviews of randomised trials (last 20 years).

#### Language

Only papers available in English were included.

Where there was insufficient information available in the reported study(ies) or review(s) to allow judgements as to whether it met the inclusion criteria, the study/review was excluded.

### Information sources and search strategy

Studies were identified by searching the following databases: Excerpta Medica database (Embase), MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR) and the WHO International Clinical Trials Registry Platform (ICTRP).

Databases were searched from December 2019 to April 2020 using a comprehensive search strategy modified for each database based on database-specific medical subject headings. The search strategies used are available in the online supplemental information.

#### Identification of studies

FQ and DD carried out independent screening of titles and abstracts for eligibility. Full-text papers were retrieved and reviewed to determine their eligibility for inclusion independently by DD and FQ with any disagreements discussed with a third reviewer, PH. We excluded protocols and ongoing trials from this review.

#### Data extraction

The data extracted from each study included study design, author details, year and journal of publication, the country in which the study was conducted, targeted condition, criteria for the diagnosis of NE, interventions under investigation and all outcomes as they are reported in the studies (including the time points). Extracting the country where the trial was conducted or the country where the lead author lived

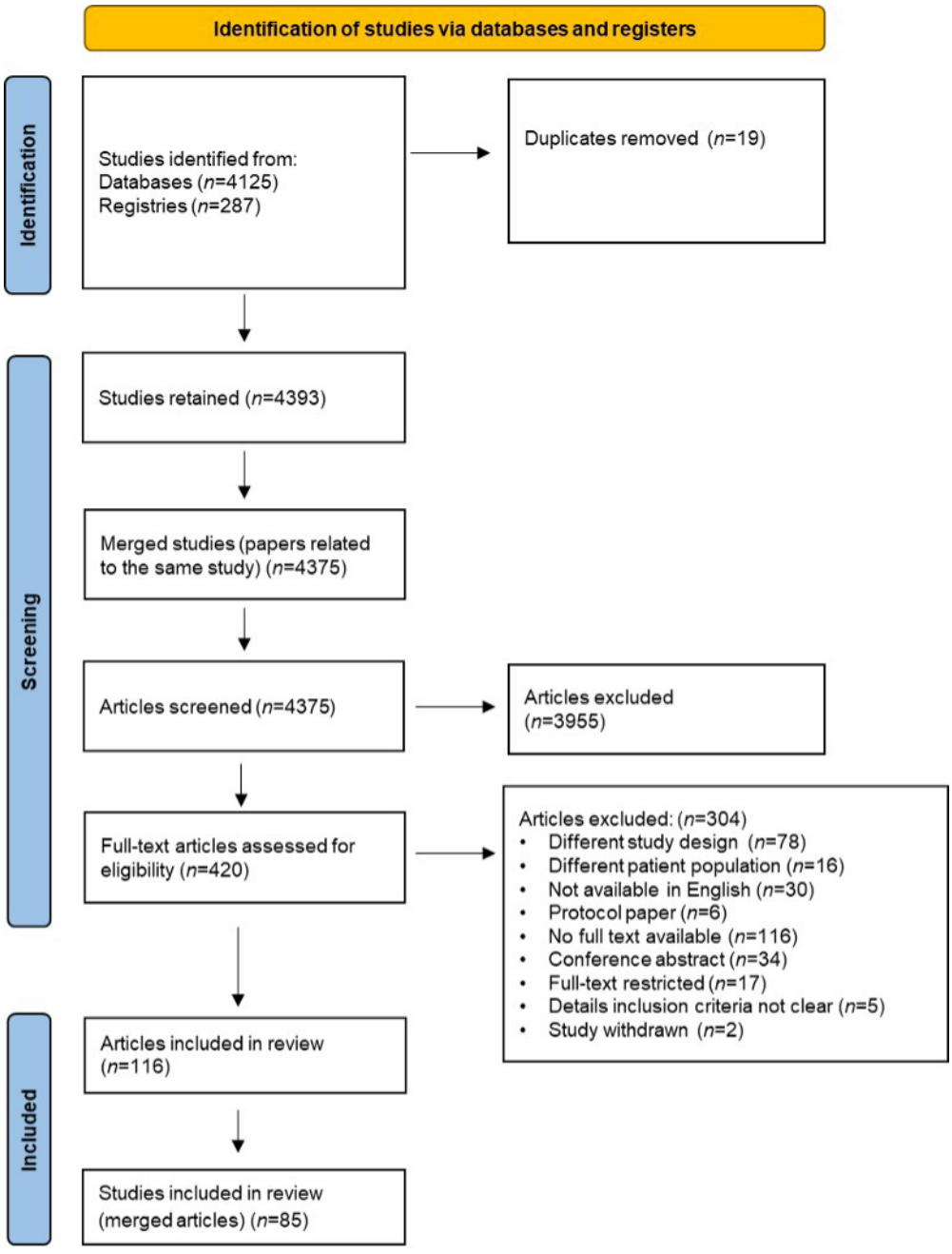


**Figure 1** COHESION Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagram.

allowed us to determine any potential differences in outcomes between high and low- to middle-income countries (LMICs). FQ extracted the data while the second reviewer (EF) conducted a verification check of 50% of the outcomes extracted against the source paper. Any discrepancies found were verified by DD. Disagreement was resolved through discussion with a third reviewer (DD).

### Data analysis and presentation

Data were tabulated so that each study and all outcomes measured in each study were displayed separately. Outcomes were grouped with similar outcomes under major domains (ie, neurological outcomes, cardiovascular outcomes, respiratory outcomes, gastrointestinal outcomes, motor development, other organ outcomes, cognitive development, development (special senses), development (speech and social), development (psychosocial), long-term disability, hospitalisation, adverse events, survival/living outcomes, healthcare utilisation, patient-reported outcomes, infection outcomes, parent-important outcomes), as guided by similar COS in this area.[24 25] Outcomes and their domains identified from the systematic review were reviewed by the COHESION Steering Group, which includes public and patient involvement representatives. Time points of when outcomes were measured and 'how' the outcomes were measured were beyond the scope of this review and were not extracted.

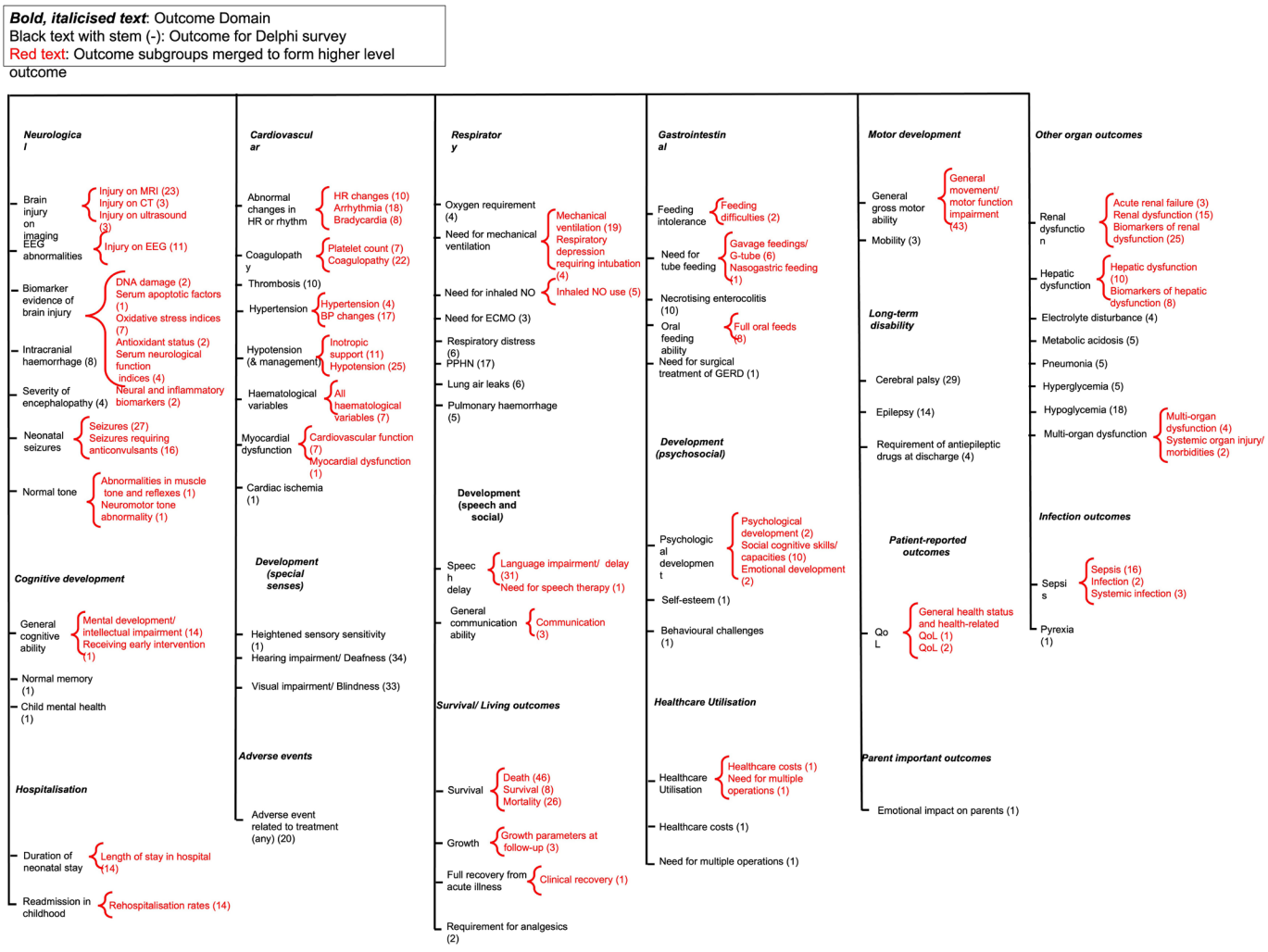


**Figure 2** Outcomes extracted from the 85 studies, outcomes merged and outcome domains identified and developed. BP, blood pressure; COS, core outcome set; GERD, gastro-oesophageal reflux disease; HR, heart rate; QoL, quality of life; NO - nitric oxide; ECMO, extracorporeal membrane oxygenation; PPHN, Persistent pulmonary hypertension of the newborn.

# RESULTS

## Study selection

Overall, 4412 citations were imported for screening from MEDLINE, Embase, CENTRAL, CDSR and the WHO-ICTRP registry, 19 of which were removed as duplicates. These were initially grouped into 4375 studies. At title and abstract screening, 3955 titles were excluded as not meeting the PICOS inclusion criteria, and 420 articles were deemed eligible for full-text screening. A further 304 full-texts were excluded for various reasons including different study designs (n=78); different patient populations (n=16); not available in English (n=30); protocol paper (n=6); no free full text available or reply from the author in response to request for full text (n=116); conference abstract (n=34); full-text restricted (n=17); details inclusion criteria not clear (n=5); study withdrawn (n=2). There were 116 articles comprising 85 studies in the data extraction process as summarised in the COHESION PRISMA diagram (figure 1).

## Characteristics of studies

This review included 62 randomised trials, 10 systematic reviews, 6 systematic reviews and meta-analysis, 6 meta-analysis and 1 review of systematic reviews. In the reviews and/or meta-analyses, 11 of the first authors were from LMICs and 12 were from high-income countries. Treatments from the 62 randomised trials included therapeutic hypothermia alone, adjuvants to therapeutic hypothermia (melatonin, xenon, darbepoetin, allopurinol, magnesium sulfate, erythropoietin and topiramate), alternative treatments to therapeutic hypothermia (melatonin, ascorbic acid and ibuprofen, phenobarbital, allopurinol, magnesium sulfate, magnesium sulfate and melatonin, erythropoietin, topiramate, monosialoganglioside vs citicoline, pyritinol) or alternative therapy such as fluid restriction.

In total, 386 outcomes were reported across 116 papers.[8 26–128] Once duplicates were removed, 66 outcomes deemed similar were categorised under 18 domains as illustrated in figure 2. The number

of domains and the number of outcomes identified in this review reflect the heterogeneity of outcomes reported in trials for the treatment of NE. Some outcomes were more commonly reported in studies. For example, brain injury on imaging was reported in 29 studies, survival was reported in 80 studies and general gross motor ability was reported in 43 studies. In contrast some outcomes, for example, the need for surgical treatment of gastro-oesophageal reflux disease and healthcare costs were reported in single studies.

Although time points were not extracted, it was noted that for some outcomes, for example, injury indicated on MRI, multiple different time points were reported for measuring the outcome, leading to further heterogeneity in outcome reporting. The terminology used to describe outcomes also varied as death, mortality and survival were used to describe the same outcome across many studies.

'Adverse events' were reported in 20 studies. Some adverse events were reported as outcomes in some studies, for example, renal dysfunction. Among the 85 studies included in this review, only one meta-analysis[49] reported outcomes of interest to patients and clinicians, described as cerebral palsy or survival with normal neurological function. However, the authors did not state how they determined these outcomes were important to patients and clinicians.

## DISCUSSION

This systematic review, identifying the outcomes measured and reported in treating NE/perinatal asphyxia/hypoxic-ischaemic encephalopathy across 85 studies, illustrates the differences in outcomes reported among studies. No outcome was measured in all studies, and 11 outcomes were only measured in a single study. This level of heterogeneity in the outcomes measured and reported in studies contributes to large amounts of research waste. It also hinders the ability to synthesise trial results to compare and contrast interventions.

Systematic reviews are used in COS development to identify the outcomes considered important to clinicians and researchers.[21] However, the benefits of including the perspectives of patients and/or parents and caregivers of patients in this process are also recognised to ensure the inclusion of outcomes they consider important for their health and the health of their children.[129] We found that only one meta-analysis included data on outcomes of interest to both patients and clinicians. Parents/caregivers of patients have different priorities on outcomes they consider to be important[130] and it is therefore essential that patients'/parents' views should be included in the selection of outcomes for randomised trials. In our qualitative interviews,[130] 25 parents identified 21 outcomes as important that were not measured and reported in the randomised trials included in this systematic review. For this qualitative study, saturation was defined as when no new outcomes were identified as the interviews and analysis progressed.

These findings highlight the need to develop a COS to be used in all studies evaluating interventions for the treatment of NE. A COS will ensure consistency in reporting the results of trials for the treatment of NE. Developing a COS ensures that measured outcomes are relevant to healthcare providers, researchers, patients and the parents of infants diagnosed with and treated for NE.

While we acknowledge that the search strategy for our systematic review was conducted in 2019, we suggest that the extent of heterogeneity in outcomes reported is unlikely to have changed substantially in more recent trials (Wu *et al*, 2022; Salamah *et al* 2023).[17 131] First, the absence of a COS for NE means that researchers need more guidance on what outcomes to select and report, making it unlikely that the heterogeneity has decreased spontaneously over a short period. Second, the issue of outcome heterogeneity is deeply rooted in the diverse clinical presentations of the condition and the varied methodologies employed across studies. These factors are unlikely to have changed significantly in a short time frame. Third, our review serves as a baseline assessment that underscores the pressing need for developing a COS for interventions for treating NE. This need would remain pertinent even if some heterogeneity reduction has occurred in recent years. Therefore, while the age of the search may be considered a limitation, the fundamental issue of outcome heterogeneity we have identified will likely remain a persistent challenge in the field until a COS is developed and implemented.

## CONCLUSION

This review highlights the heterogeneity in outcome reporting across studies looking at interventions for treating NE. The manner in which outcomes are described also varied across studies, highlighting the need for consistency. This heterogeneity warrants the development of a COS for interventions for treating NE. This review demonstrates the benefits of a COS in studies evaluating treatments for NE, as this will support the reduction of research waste and allow improved synthesis of trial results.

**Author affiliations**
[1]Neonatal Encephalopathy PhD Training Network, Health Research Board, Dublin, Ireland
[2]Health Research Board -Trials Methodology Research Network (HRB-TMRN), University of Galway, Galway, Ireland
[3]School of Medicine, University of Limerick, Limerick, Ireland
[4]School of Nursing & Midwifery, University of Galway, Galway, Ireland
[5]Evidence Synthesis Ireland, University of Galway, Galway, Ireland

[6]Auckland City Hospital, Auckland, New Zealand
[7]Liggins Institute, University of Auckland, Auckland, New Zealand
[8]Advocacy and Policymaking Irish Neonatal Health Alliance, Wicklow, Ireland
[9]Centre for Biostatistics, Manchester Academic Health Science Centre, Manchester University, Manchester, UK
[10]Paediatrics, Trinity College Dublin, Dublin, Ireland
[11]Paediatrics, Tallaght Hospital, Dublin, Ireland
[12]Department of Obstetrics and Gynecology, Indiana University, Bloomington, Indiana, USA
[13]Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK
[14]Irish Neonatal Health Alliance, Wicklow, Ireland
[15]Grace Centre for Newborn Care, The Children's Hospital at Westmead, Sydney, New South Wales, Australia
[16]The University of Sydney, Sydney, New South Wales, Australia
[17]Academic Neonatal Medicine, Imperial College London, London, UK

**X** Fiona Quirke @Fiona_Quirke_ and Mandy Daly @irishneonatal

**Contributors** FQ, DD and EM conceived the study. All authors contributed to the systematic review study protocol development, implementation and analysis. FQ, EF and DD coordinated the review and FQ, PH and DD drafted the manuscript. All authors commented on revisions to draft versions of this manuscript and read, commented on and approved the final manuscript. FQ is guarantor for this manuscript.

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**ORCID iDs**
Fiona Quirke http://orcid.org/0000-0001-9155-5543
Malcolm Battin http://orcid.org/0000-0001-9622-0523
Frank Harry Bloomfield http://orcid.org/0000-0001-6424-6577
Mandy Daly http://orcid.org/0000-0001-7539-4874
Jamie J Kirkham http://orcid.org/0000-0003-2579-9325
Karen Walker http://orcid.org/0000-0002-4149-2270
James Webbe http://orcid.org/0000-0001-8546-3212

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