Consensus definition and Diagnostic Criteria for Neonatal Encephalopathy – Study Protocol for a Real-Time Modified Delphi Study

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Abstract

Background

Neonatal encephalopathy (NE) describes a group of conditions presenting in term infants as disturbed neurological function. One cause is hypoxic ischaemic encephalopathy. There is a lack of consensus and uniformity in terminology used to describe the condition and the criteria by which it is diagnosed. This creates difficulty in design of research and complicates communication with families. The DEFINE study aims to use a modified-Delphi approach to form a consensus definition and set of diagnostic criteria for NE.

Methods

After conducting a systematic review of existing literature to assess use of terminology in trials of NE, an international steering group will be formed. Under guidance of the steering committee, an online Real-time Delphi survey for the definition and diagnostic criteria of NE will be completed. A consensus meeting to agree on the final terminology and criteria will be held. The outcome of this consensus process will be disseminated widely to aid implementation.

Discussion

The lack of uniformity and consensus on terminology for NE and the sub-categories create difficulty in communication and research design. Introducing a consensus-based definition using a modified-Delphi technique will be valuable to improve communication with families and between professionals and ultimately positively impact patient care.

Introduction

Neonatal Encephalopathy (NE) refers to disturbed neurological function of any type in a newborn baby [1]. Infants with NE can have difficulty initiating and sustaining respiration and may need resuscitation at delivery. They will have an abnormal neurological examination including low tone, reduced level of consciousness, decreased or absent primitive reflexes and may have seizures. Infants may also have difficulty feeding due to poor tone and a weak or absent suck reflex. The American Academy of Pediatrics has defined NE as a 'clinical syndrome of disturbed neurologic function in the earliest days after birth in an infant born at or beyond 35 weeks of gestation, manifested by a subnormal level of consciousness or seizures, often accompanied by difficulty with initiating and maintaining respiration, and depression of tone and reflexes'[2].

NE is a clinical diagnosis which must be made in the first hours of life. The only effective interventional therapy for therapeutic hypothermia with a presumed hypoxic ischaemic aetiology is therapeutic hypothermia, which is most effective when initiated within six hours of birth [3]. Therapeutic hypothermia, or induced cooling, is when the newborn's body temperature is cooled to 33 +/- 0.5 degrees Celsius for 72 hours to protect the brain from secondary injury. It has been shown to reduce the risk of death or major neurodevelopmental disability at 18 months of age, with a number needed to treat of 7, and conversely to improve survival without disability [3].

Hypoxic ischaemic encephalopathy (HIE) is the cause of approximately 50% of cases of NE, where the aetiology of the brain injury underlying the encephalopathic presentation is a decreased supply of oxygen in the perinatal period. As suggested by the AAP, the diagnosis of HIE is most appropriately made retrospectively, after several aetiological investigations are complete, and in the presence of a sentinel event likely to cause hypoxia, e.g., placental abruption, cord accident, uterine rupture, among others [2].

The other 50% of cases of neonatal encephalopathy are made up by multiple rarer diagnoses, including but not limited to: metabolic and genetic causes, congenital neuromuscular disorders, infection or sepsis and neonatal stroke [1, 4]. In practice, many of these cases will be multifactorial, while in some cases, despite thorough investigation, the cause will remain unclear (figure 1). The ultimate diagnosis will depend on the result of placental examination, genetic and metabolic investigations, investigation for sepsis or meningitis where indicated, neuro-imagining investigations as well as a thorough investigation of the obstetric course, delivery, and postnatal events [4] (figure 1).

The terminology in neonatal brain injury, namely NE, HIE and perinatal asphyxia (PA), tend to be interchangeable in the literature and in discussions among clinical staff and with families. The definitions underlying these terms can vary across studies and publications, creating confusion between professionals and families and difficulty in comparison of data and meta-analysis of results.

The pre-existing definitions of NE, PA and HIE are not broad enough to encapsulate the full spectrum of NE, excluding those infants who do not meet the criteria for therapeutic hypothermia, those infants with mild NE and infants under 35 weeks of gestation. While these babies may not be appropriate candidates for currently available therapies, they are at higher risk of poor neurological and developmental outcomes than their peers and may benefit from treatments that become available in the future [5].

Therefore, an international evidence-based consensus definition is required to define NE and the diagnostic criteria required to diagnose the condition. This will lead to the possibility of accurately defining the subgroups of NE and the diagnostic criteria to meet each diagnosis. The aim of the DEFINE project, as outlined by the steering group of the project, an international group

of experts in NE, including parent representatives, is the development of an international multidisciplinary consensus definition, using a Delphi consensus approach.

Methods/Design

The development of this definitional statement and set of diagnostic criteria will adhere to the ACCORD guideline for reporting consensus-based methods without a definitive set of recommendations on forming consensus-based definitions or diagnostic criteria [6]. We will also base our work on the methods employed by our group previously in the consensus-based development of definitions for other disease processes and core outcome sets and those outside our group [7-9].

This work will be carried out in five phases.

Phase 1: We will establish a steering group for the project involving experts in Neonatal Encephalopathy (NE)

Phase 2: In parallel with the formation of the steering group, a systematic review of the literature will be performed to identify the definition/inclusion criteria used in previously published literature on trials evaluating the effectiveness of interventions for managing Neonatal Encephalopathy

Phase 3: Online Real-time Delphi survey – a number of domains, each with an included set of definitional statements will be put forward for voting for inclusion/exclusion in the definition.

Phase 4: Consensus development meeting to agree on the final wording of neonatal encephalopathy definition and set of diagnostic criteria – facilitated by the James Lind Alliance

Phase 5: Dissemination and Implementation of the consensus definition

The steering group for the Define Project will include neonatologists, neurologists, obstetricians, nurse and midwife representatives, allied health professionals, parents of infants with neonatal encephalopathy and representatives from parents' groups (i.e. public and patient involvement representatives), experts in research methodology, and clinical and scientific researchers in neonatal encephalopathy. We will endeavour to have input from both high and low-middle-income countries and a broad geographical spread. The collective knowledge of this group will inform the creation of the Delphi Study and the development of the definition/diagnostic criteria.

Phase 1: Development of steering committees

A steering committee will be formed, including international experts in the field of neonatal intensive care, neonatal and paediatric neurology, parent and patient representatives and healthcare research methodology. The James Lind Alliance will be involved as part of the steering committee and invited to act as experts in the design and running of and facilitators for the consensus development meeting. Ethical approval for the project will be obtained before commencing from the Ethics Committee of The Coombe Hospital, Dublin, Ireland.

Phase 2: Systematic Review

Research question: What descriptive terminology and definitions are used in clinical trials of Neonatal Encephalopathy

We will conduct a systematic review of randomized trials evaluating the effectiveness of interventions used for treating Neonatal Encephalopathy, to identify the descriptive term(s) used

to identify Neonatal Encephalopathy/Perinatal Asphyxia/Hypoxic Ischaemic Encephalopathy and the definition/diagnostic criteria used in each trial. This study was developed as an extension of a registered protocol with Prospero (CRD42020170265), a systematic review of reported outcomes in randomized control trials in Neonatal Encephalopathy.

Inclusion Criteria

Types of Studies – Randomized trials evaluating the effectiveness of interventions for treating Neonatal Encephalopathy.

Types of Participants – Infants with a reported clinical diagnosis of and receiving treatment for Neonatal Encephalopathy or Hypoxic Ischaemic Encephalopathy, with a gestational age greater than 35 weeks. Any definition of Neonatal Encephalopathy/Hypoxic Ischaemic Encephalopathy/Perinatal Asphyxia that includes features of perinatal asphyxia or encephalopathy will be acceptable.

Types of Intervention – Any intervention to treat neonatal encephalopathy or HIE. Comparison/control group may be an alternative intervention, placebo treatment or control (no treatment) group.

Types of Outcomes – Description of the terminology, definitions and diagnostic criteria used to describe term infants who are encephalopathic after birth and their frequency of use within clinical trials of interventions.

Search Methodology

Five databases will be systematically searched i.e. Embase, Medline (pubmed), the Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic

Reviews (CDSR) and the World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP) – ongoing trials. Searches will be restricted to the last 20 years. Additional references will be identified via reference searching and discussion with experts in the area.

Assessment for eligibility

The titles and abstracts of each citation identified by the search strategy will be screened independently by two reviewers. Full-text examination will be carried out on potentially relevant citations. Disagreements will be resolved through discussion with a third reviewer.

Data Extraction

Data will be extracted from each study into a purposefully designed data extraction form, including study design, author details, year, journal of publication, the country in which the study was conducted, term used for the targeted condition, the definition used for this term, criteria for the diagnosis of target condition, interventions under investigation and outcomes. Data will be extracted independently by two individual reviewers. Disagreement will be resolved through discussion with a third reviewer.

Data analysis and presentation

Data will be tabulated using an excel spreadsheet. No meta-analysis is proposed for this review. The terminology used will be divided into perinatal asphyxia, Neonatal Encephalopathy and hypoxic ischaemic encephalopathy. Data will be grouped into perinatal asphyxia and neurological assessment categories. All quantitative analyses will be conducted with SPSS software.

Phase 3: Online Realtime Delphi Survey

The Delphi method has been used widely and successfully to achieve consensus among experts since its development in the 1960s. It has been successfully employed in several areas of medicine to achieve consensus on core outcome sets and definitions, among others [8-10]. The traditional Delphi approach uses an iterative process with repeated rounds of evaluation and voting, with feedback provided between rounds to arrive anonymously at a consensus. The Real-time method was developed to decrease the time taken and risk of participant attrition seen in traditional Delphi methods. In this round-less method, participants can view the group response in real-time after responding and revisit and re-rate responses based on group feedback [11]. The Realtime Delphi approach has been successfully used in the medical fields [12, 13] and the results of a randomized trial of the traditional approach and real-time approach for developing a core-outcome set in Neonatal Encephalopathy are awaited [14].

Design:

The identified publications from the systematic review will inform the Delphi process. Members of the working group will review each identified paper. The definition used in each paper will be identified and the language and features used to characterize neonatal encephalopathy/hypoxic ischaemic encephalopathy or perinatal asphyxia will be extracted. Each definition will be structured into several domains (for example evidence of perinatal asphyxia, neurological assessment) based around common themes found within the identified definitions. Within each domain, we will form several statements, ideas or concepts covering different aspects within the domain and covering the breadth of opinion on what may be considered valuable for inclusion. Respondents will first vote on their opinion of the domain as a whole, before voting on the definitional statements within.

The steering committee will assess and approve the contents of the Delphi questionnaire before commencement of the online process, with the potential to add domains or statements as appropriate.

Setting:

The consensus process will take place online. Calibrum (Surveylet) software (https://calibrum.com) will be used to facilitate the real-time aspect based on the results of studies comparing software platforms [15, 16].

Consent:

Participants will be asked to provide informed consent after reading the participant information leaflet and before commencing the process. Before participation, they will be asked to complete a short demographic survey (stakeholder group, level of experience, country of work, ethnicity and basic demographic details).

Participants and Recruitment:

We will recruit participants with expertise in NE from a broad range of stakeholder groups. These include healthcare providers (neonatologists, neurologists, obstetricians, midwives, neonatal intensive care nurses, allied health professionals), researchers and parents/family members/guardians of children with neonatal encephalopathy or adults who had NE as infants. We will disseminate an invitation to participate to target participants via a number of channels. We will use electronic discussion lists, contact those who have previously participated in similar research work carried out by this group, and contact experts who have published in this area identified through the systematic review, professional organizations, and parent/family support networks and organizations.

Purposeful sampling will be used to ensure that participants representing each stakeholder group from both high and low-to-middle-income countries are recruited. We will ensure participation of each group of stakeholders at each stage of the consensus process. Participants will be grouped broadly into three groups: a) parents/family members/guardians of infants who received care for NE, b) healthcare providers, and c) researchers and policymakers. The survey will be live for a 4-month period, and we aim to recruit at least 100 participants during this time.

In the real-time Delphi, participants will be asked their opinion on what is important to include or exclude in a definition of NE. They will do so for each domain initially and then each statement within that domain using a 5-point Likert scale (strongly agree with inclusion/agree with inclusion/need more information or clarification/disagree with inclusion/strongly disagree with inclusion).

For each domain and statement, the participant can view their rating of the item, the overall rating of the item and the rating of the item for each stakeholder group immediately after rating the item for the first time. After viewing the feedback, the participant can, if they choose, modify their response before moving to the next item.

A free-text box will be provided alongside each domain/statement that the respondent is asked to vote on. The participant can use this to add additional detail they feel pertinent to include, clarify reasoning, or propose alternative wording if they agree with the premise of the statement overall but not the exact wording. The participants will be able to view the comments made by other participants in real time, identified by stakeholder group – as it may benefit other participants to understand the area of expertise of those providing comments. If participants would prefer to remain anonymous only stakeholder group will be reported. Participants will also be able to suggest additional statements that they feel should be added to each domain.

Participants can save their responses and revisit them before the pre-determined completion date. As the degree of consensus changes, depending on each additional rating, we will encourage participants via email reminders to revisit the survey and review their answers. No new participants will be recruited the week before the completion date to ensure adequate time for engagement with the process. The working group will decide the timing and frequency of email reminders based on temporal responses and level of engagement.

The order in which the domains and its associated statements are presented to participants will be randomized to decrease the influence of order on question responses [17]. Medical terminology will be used in each statement where relevant, with a plain-language summary provided to participants. To avoid a small group of initial participants having a significant influence on consensus levels and potentially biasing early participants, a representative group from each stakeholder group, and members of the steering committee, will vote on each item before the real-time Delphi goes live. In this way, consensus information will be provided to each online participant in the same manner.

An 80% consensus threshold will be used for the inclusion and exclusion of statements in the final definition – if there is agreement by 80% of participants overall on a statement, it will be included/excluded. An 80% threshold was used based on previous similar work and evidence from the literature that suggest 80% agreement is needed for validity in consensus in groups of greater than ten experts [18].

The working group will follow the progress of the real-time Delphi process. If necessary, the process will be paused to allow for analysis of responses, clarification of statements or addition of statements suggested by participants and removal of those reaching consensus. After pausing to allow this, the process will be recommenced for participants as outlined above. If several

potentially contradictory statements are identified, these will be grouped, and participants will be asked to vote on their level of agreement with each statement.

Phase 4: Consensus meeting

Objective: The aim of the consensus meeting will be to achieve final agreement on the wording of one unifying definition for the term NE, and a set of diagnostic criteria for NE, based on the findings of the Delphi consensus process through online meetings of international stakeholders with expertise in NE.

We will hold two independent consensus meetings with different stakeholders, including at least three people from each stakeholder group (clinicians, parent and patient representatives, scientists and policy makers).

During the meetings, the outcomes emerging from the real-time Delphi will be presented to the participants along with the voting patterns of the stakeholder groups for each domain/statement. An experienced facilitator will chair each consensus meeting. There will be anonymous computerised voting after a discussion on any domain or statement which has not already reached the identified threshold of 80% for inclusion or exclusion from the Delphi survey. The domains and statements will be formulated into the final definition, the exact wording of which will be discussed and agreed at the consensus meeting. The James Lind Alliance will be involved in designing and running the consensus development meetings.

Phase 5: Dissemination and Implementation Strategy

Our dissemination and implementation plan will be guided by the Health Research Board (HRB, Ireland) knowledge transfer strategy, i.e., (i) Monitor; (ii) In-form; (iii) Knowledge Exchange; (iv) Persuade; (v) Network and (vi) Support. The outcome of our consensus process,

including the definition itself and set of diagnostic criteria, will be published in an international peer-reviewed open-access journal. We will present our definition at international meetings of experts in this field and disseminate our findings via other channels, including clinical trial networks and units, and research funding agencies.

Discussion

Neonatal encephalopathy is an umbrella term describing brain injury in the term newborn. Despite several organizations advocating for the use of the term NE, and then a more precise causative diagnosis, be that hypoxic ischaemic encephalopathy or another, being applied after thorough aetiological investigations have been performed [2]. The terms NE, HIE and PA have been used interchangeably and sometimes without definition in the literature to convey an infant with a brain injury from birth. This leads to difficulty in identifying the group of patients enrolled in a clinical trial and therefore the potential generalisability of the findings and meta-analysis of the results given the heterogeneity of the primary literature. As the search for adjunctive treatments to therapeutic hypothermia, or indeed standalone therapies for use in low-middle income counties goes on, the use of a standard term with a standard definition may aid the development of these trials and implementation of their results. For parents and caregivers of infants with NE, using consistent terminology and meaning for these terms will aid with understanding, aetiological diagnosis and access to the correct support available to them. The Delphi process has been used previously to provide consensus among large groups of experts. Our modified Realtime Delphi approach has been successfully employed to develop consensus. This protocol provides a consensus-based definition and set of diagnostic criteria for the term neonatal encephalopathy,

which will be accepted and utilised by the neonatal community to improve research, outcomes, and parental experience.

Trial Status

Currently, this project is moving through phases 1-3 as outlined in the above protocol. The systematic review of phase 1 is being analysed and finalized. A steering group has been formed, and preliminary meetings have been held to define the scope of our process and finalize this protocol. Ethical approval has been obtained for the project from the ethics committee of the Coombe Woman and Infants University Hospital, Dublin (REC number 13-2022).

Declarations: The authors have no conflicts of interest to disclose.

Ethical Approval: Ethical approval has been obtained for the project from the ethics committee of the Coombe Woman and Infants University Hospital, Dublin (REC number 13-2022).

Consent to participate: Informed consent will be obtained via the online software platform prior to beginning participation in the study.

Availability of data and materials: Data can be made available on reasonable request to the corresponding author

Competing interests: No author has a competing interest to declare.

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Authors contributions: EM, DD, AB, TH and FQ conceived and designed this project. AB, DD and EM drafted the initial draft of the protocol and manuscript. All authors attended meetings of the steering committee of the DEFINE group and were involved in the design of the above protocol. All authors critically revised the manuscript. All authors reviewed and approved the final manuscript.

Figure Legends

Figure 1 .

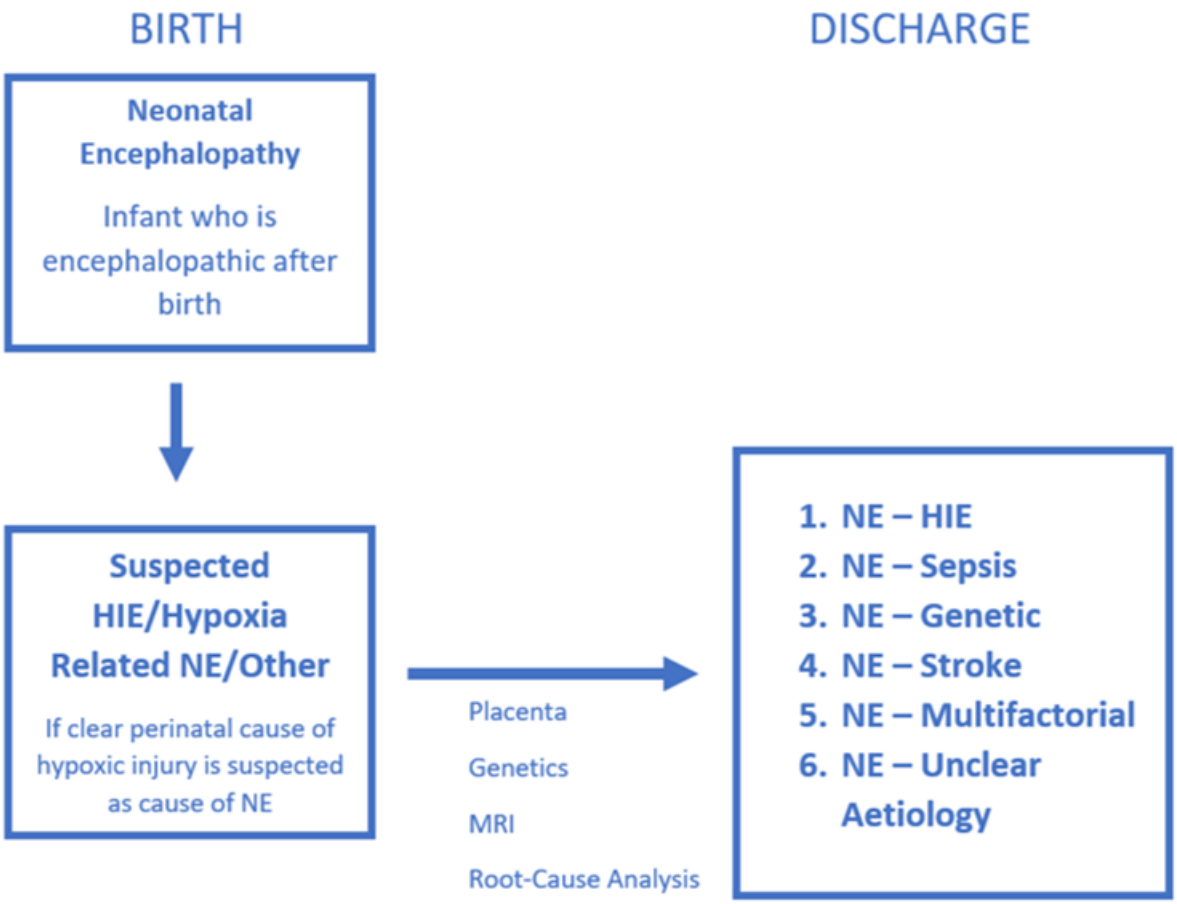

Figure 1. A scheme representing movement from the initial umbrella diagnosis of 'Neonatal Encephalopathy' to a final aetiological diagnosis after appropriate investigation and analysis is carried out.

References

1. Aslam, S., T. Strickland, and E.J. Molloy, *Neonatal Encephalopathy: Need for Recognition of Multiple Etiologies for Optimal Management.* Front Pediatr, 2019. **7**: p. 142.
2. *Executive summary: Neonatal encephalopathy and neurologic outcome, second edition. Report of the American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy.* Obstet Gynecol, 2014. **123**(4): p. 896-901.
3. Jacobs, S.E., et al., *Cooling for newborns with hypoxic ischaemic encephalopathy.* Cochrane Database Syst Rev, 2013. **2013**(1): p. Cd003311.
4. Martinello, K., et al., *Management and investigation of neonatal encephalopathy: 2017 update.* Arch Dis Child Fetal Neonatal Ed, 2017. **102**(4): p. F346-f358.
5. Chalak, L.F., et al., *Prospective research in infants with mild encephalopathy identified in the first six hours of life: neurodevelopmental outcomes at 18-22 months.* Pediatr Res, 2018. **84**(6): p. 861-868.
6. Gattrell, W.T., et al., *ACCORD guideline for reporting consensus-based methods in biomedical research and clinical practice: a study protocol.* Research Integrity and Peer Review, 2022. **7**(1): p. 3.
7. Quirke, F.A., et al., *COHESION: core outcomes in neonatal encephalopathy (protocol).* Trials, 2021. **22**(1): p. 125.
8. Allen, J., et al., *Severe Neurological Impairment: A delphi consensus-based definition.* Eur J Paediatr Neurol, 2020. **29**: p. 81-86.
9. Swedo, S.E., et al., *Consensus Definition of Misophonia: A Delphi Study.* Front Neurosci, 2022. **16**: p. 841816.

10. Turoff, M., *The design of a policy Delphi.* Technological Forecasting and Social Change, 1970. **2**: p. 149-171.

11. Gordon, T. and A. Pease, *RT Delphi: An efficient, "round-less" almost real time Delphi method.* Technological Forecasting and Social Change - TECHNOL FORECAST SOC CHANGE, 2006. **73**: p. 321-333.

12. Nabergoj Makovec, U., et al., *Developing a medication adherence technologies repository: proposed structure and protocol for an online real-time Delphi study.* BMJ Open, 2022. **12**(4): p. e059674.

13. Garner, B.R., et al., *The Prevalence and Negative Impacts of Substance Use Disorders among People with HIV in the United States: A Real-Time Delphi Survey of Key Stakeholders.* AIDS Behav, 2022. **26**(4): p. 1183-1196.

14. Quirke, F.A., et al., *Multi-Round compared to Real-Time Delphi for consensus in core outcome set (COS) development: a randomised trial.* Trials, 2021. **22**(1): p. 142.

15. Aengenheyster, S., et al., *Real-Time Delphi in practice — A comparative analysis of existing software-based tools.* Technological Forecasting and Social Change, 2017. **118**: p. 15-27.

16. Varndell, W., M. Fry, and D. Elliott, *Applying real-time Delphi methods: development of a pain management survey in emergency nursing.* BMC Nursing, 2021. **20**(1): p. 149.

17. Brookes, S.T., et al., *Impact of question order on prioritisation of outcomes in the development of a core outcome set: a randomised controlled trial.* Trials, 2018. **19**(1): p. 66.

18. Lynn, M.R., *Determination and quantification of content validity.* Nurs Res, 1986. **35**(6): p. 382-5.