Establishing Surrogate markers by Consensus for Antepartum and Intrapartum Stillbirth: The In-utero Consensus for Alternative outcomes in Research on Stillbirth (ICARES) project

Sanne Gordijn[1], Aris Papageorghiou[2], Anna David[3], Sam Ali[4], and Wessel Ganzevoort[5]

[1]Universitair Medisch Centrum Groningen
[2]St George's University Hospitals NHS Foundation Trust
[3]University College London Faculty of Population Health Sciences
[4]Makerere University School of Medicine
[5]Amsterdam UMC Locatie AMC

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Abstract

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AUTHORS: Sanne J Gordijn*[1], Aris T Papageorghiou*[2,3], Anna L David[4,5], Sam Ali[6], Wessel Ganzevoort[7,8]

1 Department of Obstetrics and Gynecology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

2 Fetal Medicine Unit, St George's University and St George's University Hospitals NHS Foundation Trust, London, UK.

3 Nuffield Department of Women's and Reproductive Health, University of Oxford, Oxford, United Kingdom

4 Elizabeth Garrett Anderson Institute for Women's Health, Faculty of Population Health Sciences, Medical School Building, University College London, 74 Huntley Street, London, WC1E 6AU, UK.

5 Women's Health Division, Elizabeth Garrett Anderson Wing, University College London Hospital NHS Foundation Trust, 25 Grafton Way, London, WC1E 6DB, UK.

6 School of Medicine, Makerere University College of Health Sciences, P.O Box 7072, Kampala, Uganda.

7 Department of Obstetrics and Gynecology, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

8 Amsterdam Reproduction & Development Research Institute, Amsterdam, The Netherlands

* SJG and ATP are joint first authors

Corresponding author: Sanne J Gordijn, s.j.gordijn@umcg.nl,

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Introduction:

Intervention bias refers to a systematic difference in management or variable exposure among subjects in studies, which can significantly influence outcomes. In the context of stillbirth research, the identification of high-risk profiles leads to modified management of pregnancies aimed at reducing stillbirth incidence. From a scientific perspective, therefore, it is crucial to identify near-misses: the stillbirths that would have occurred if management had remained unchanged.

The Wellcome Leap In Utero program (https://wellcomeleap.org/inutero/), with its goal to tackle the global issue of stillbirth, endeavors to develop scalable capacity for accurate measurement, modeling, and prediction, with the aim of halving stillbirth rates without increasing provider-initiated delivery within the next 5-10 years. Fifteen programs were selected to collaboratively improve the identification of at-risk fetuses using various technologies. During the Principal Investigator (PI) meeting held in Horsley, UK, from March 5-7, 2023, a time-condensed Delphi consensus procedure was employed to address the need for synchronized stillbirth near-miss definition.

Methods:

All rounds were conducted using Google Forms, with the first three rounds occurring within a 24-hour period during the PI meeting. The first round involved collecting demographic information and obtaining informed consent. Potential surrogate markers were identified through an open-ended question.In the second round, participants were presented with a feedback report that introduced the subsequent phase. The suggested surrogate markers were categorized as antenatal, maternal, neonatal, or placental markers, with overlapping variables consolidated. Each marker was then ranked on a scale from very important (5) to irrelevant (1), with the option for non-medical scientists to selectively choose 'no opinion'. The third round involved participants indicating agreement on marker inclusion. A median score of 5 indicated inclusion, a median score of 4 indicated potential inclusion, a median score below 4 indicated exclusion. Consensus was reached when 70% agreement was achieved. A follow-up online round was conducted after 3 months to confirm the condensed final list of surrogate markers and identify the measurement instruments to be used, requiring 80% agreement for consensus.

Results:

The four rounds of the consensus procedure garnered participation from 31, 33, 31, and 29 individuals, respectively. A significant majority (97%) agreed on the necessity of reaching a consensus. Initially, 91 markers were suggested, eventually leading to the agreement on six overarching markers and their corresponding measurement instruments, as presented in Table 1.

Table 1

[A] Using INTERGROWTH-21ST newborn size charts(1)

[B] According to Delphi consensus definition(2)

[C] Severe brain injury diagnosed < 7 days of life; therapeutically cooled/decreased central tone/comatose/seizures of any kind/ amplitude integrated electroencephalography abnormality <24 hours of birth.

[D] Using ISSHP definition(3) (amended: 'despite maintenance treatment with multiple (*instead of 3*) anti-hypertensive agents', plus pre-eclampsia arising at less than 34 weeks gestation)

[E] Using the Amsterdam consensus criteria(4) or Freedman classification.

Conclusions:

In a unique setting—a live three-day meeting attended by highly-engaged, knowledgeable professionals and prinPI's in stillbirth research, with extensive consensus procedure experience—six markers for identification of near-misses in stillbirth studies were agreed upon. The importance of establishing a standardized list of surrogate markers for use by all research groups was recognized. Some limitations should be acknowledged: most participants were from high-income countries. Also, adverse events related to interventions leading to unnecessary preterm birth are not captured in this procedure. When risk prediction for stillbirth is accurate and is paired with effective interventions, stillbirth will be prevented. From the perspective of a screening study, a successful prediction-prevention coupling changes a true-positive to a false-positive, and could result in rejecting successful approaches.(5) We believe the current near-miss stillbirth outcome set is a step closer to appropriate recognition of those pregnancies in which a stillbirth was a near-miss.

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Table 1 near miss criteria.docx available at https://authorea.com/users/326353/articles/652514-establishing-surrogate-markers-by-consensus-for-antepartum-and-intrapartum-stillbirth-the-in-utero-consensus-for-alternative-outcomes-in-research-on-stillbirth-icares-project