Feasibility and design of a trial regarding the optimal mode of delivery for preterm birth: the CASSAVA multiple methods study

Jane E Norman,[1*] Julia Lawton,[2] Sarah J Stock,[2] Dimitrios Siassakos,[3] John Norrie,[4] Nina Hallowell,[5] Sushila Chowdhry,[6] Ruth I Hart,[2] David Odd,[7] Jane Brewin,[8] Lucy Culshaw,[9] Caroline Lee-Davey,[9] Hannah Tebbutt[10] and Sonia Whyte[11]

[1]Faculty of Health Sciences, University of Bristol, Bristol, UK
[2]Usher Institute, University of Edinburgh, Edinburgh, UK
[3]Institute for Women's Health, University College London, London, UK
[4]Edinburgh Clinical Trials Unit, University of Edinburgh, Edinburgh, UK
[5]Ethox Centre and Wellcome Centre for Ethics & Humanities, Nuffield Department of Population Health, University of Oxford, Oxford, UK
[6]School of Health Sciences, University of Dundee, Dundee, UK
[7]Division of Population Medicine, School of Medicine, University of Cardiff, Cardiff, UK
[8]Tommy's, London, UK
[9]Bliss, London, UK
[10]Edinburgh, UK
[11]Tommy's Centre for Maternal and Fetal Health, MRC Centre for Maternal and Fetal Health, University of Edinburgh, Edinburgh, UK

*Corresponding author jane.e.norman@bristol.ac.uk

Declared competing interests of authors: Jane E Norman has received grants from government and charitable bodies for research into understanding the mechanisms of term and preterm labour and understanding treatments, including research funding from the National Institute for Health Research (NIHR) (references 17/63/08 and 16/151/01). Within the last 3 years, Jane E Norman has acted on a Data Safety and Monitoring Board for a study involving a preterm birth therapeutic agent for GlaxoSmithKline plc (Brentford, UK) and has provided consultancy for a small pharma company on drugs to alter labour progress. In addition, Jane E Norman was a member of the Health Technology Assessment (HTA) Maternal Neonatal and Child Health Panel (2013–18) and was a member of the HTA and Efficacy and Mechanism Evaluation (EME) Editorial Board from 2012 to 2014. Julia Lawton was a member of HTA Obesity Themed Call Board (2010) and HTA General Committee (2018–19). Sarah J Stock reports grants from the NIHR HTA programme during the conduct of the study and declares being a member of the NIHR HTA General Committee (2016–21). In addition, Sarah J Stock received other research funding from the NIHR (reference 14/32/01), Wellcome Trust (London, UK) (reference 209560/Z/17/Z) and Chief Scientist Office (London, UK) during the course of the study. Dimitrios Siassakos reports grants from the NIHR HTA Research for Patient Benefit (reference PB-PG-0817-20046) and HTA programme (references 16/16/06, NIHR127818 and PR-PRU-1217-21202) during the conduct of the study. In addition, Dimitrios Siassakos reports grants from the NIHR Biomedical

Research Centre at University College London Hospitals (London, UK) and non-financial support from Wellcome Engineering and Physical Sciences Research Council Centre for Interventional and Surgical Sciences (London, UK) outside the submitted work. Last, Dimitrios Siassakos was a member of the HTA Maternal, Neonatal and Child Health Panel (2017–18), HTA Prioritisation Committee C (Mental Health, Women and Children's Health) (2017–20) and HTA Prioritisation Committee B (In Hospital) (2017–21). John Norrie reports grants from the University of Edinburgh (Edinburgh, UK) during the conduct of the study, and is a past and present member of the following: HTA Commissioning Sub-Board (Expressions of Interest) (2012–16), NIHR Clinical Trials Unit Standing Advisory Committee (2017–present), NIHR HTA and EME Editorial Boards (2014–19), Pre-Exposure Prophylaxis Impact Review Panel (2017–present), EME Strategy Advisory Committee (2019–present), EME – Funding Committee Members (2019–present), EME Funding Committee Sub-Group Remit and Competitiveness Check (2019–present), HTA General Committee (2016–19), HTA Funding Committee Policy Group (formerly Clinical Study Group) (2016–19) and HTA Commissioning Committee (2010–16). In addition, John Norrie acted as a NIHR Journals Library Editor between 2014 and 2019. Nina Hallowell is a member of the Wellcome Centre for Ethics and Humanities (Oxford, UK), which is supported by funding from the Wellcome Trust (grant number 203132).

Disclaimer: This report contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

Published November 2021
DOI: 10.3310/hta25610

Scientific summary

CASSAVA multiple methods study

Health Technology Assessment 2021; Vol. 25: No. 61
DOI: 10.3310/hta25610

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Preterm birth (PTB) (prior to 37 weeks' gestation) affects 7% of UK livebirths, and is the single largest cause of neonatal mortality and morbidity. Importantly, although survival rates have increased with time, rates of disability have remained unchanged. Despite the relatively common nature of PTB, there is significant uncertainty about which mode of birth (MoB) [vaginal or caesarean section (CS)] is best. This uncertainty was highlighted in the 2015 National Institute for Health and Care Excellence guidance on preterm labour and birth, in which clinicians were advised 'to discuss the risks and benefits of vaginal and caesarean delivery with women thought to be in preterm labour and to highlight the potential risks associated with caesarean sections' (National Institute for Health and Care Excellence. *Preterm Labour and Birth*. London: National Institute for Health and Care Excellence; 2015. © NICE 2015 Preterm Labour and Birth. Available from www.nice.org.uk/guidance/ng25. All rights reserved. Subject to Notice of rights NICE guidance is prepared for the National Health Service in England. All NICE guidance is subject to regular review and may be updated or withdrawn. NICE accepts no responsibility for the use of its content in this product/publication).

Despite this advice, the evidence base on risks and benefits is limited largely to observational studies. There is uncertainty as to whether or not a randomised trial is possible, in part because of established practice.

The research described in this monograph was in response to a Health Technology Assessment-commissioned call (17/22 'Mode of delivery for preterm infants') to:

> *. . . establish the scenarios in which there is equipoise in how best to deliver a preterm baby and to define the most important outstanding question(s) for clinicians and parents in this area that could be addressed by a future trial. If outstanding questions are identified in this first phase then researchers are asked to conduct qualitative work with clinicians and potential participants to determine the acceptability of randomisation in order to inform the feasibility of future research.*

Objective

The overall aim of the CASSAVA project was to determine whether and what sort of trial could be done to define the optimal mode of preterm birth. We planned to find the groups of women and babies in preterm labour with whom there is clinical uncertainty about the optimal planned mode of birth, and whether or not women and clinical staff would be willing to participate in a future randomised trial to address this question. We aimed to determine the specific groups of preterm women and babies where there are uncertainties about the best planned mode of birth, and where there would be willingness to recruit to/participate in a randomised trial to address some but not all of these uncertainties.

Methods

We planned a series of clinician and patient surveys and a consensus workshop/Delphi group to inform the design of a hypothetical clinical trial (HCT). We planned to devise a protocol for the HCT and a vignette for discussion with potential participants. We planned focus groups (FGs) to talk to potential participants about the trial and telephone interviews to talk to clinicians. Last, we had planned to design and cost a future trial.

Results

We broadly achieved our aims. We conducted clinician and patient surveys and the consensus workshop, achieving our planned sample size for each. These events were richly informative for the design of a protocol for a HCT (which we called CASSAVAplus) and a vignette for discussion with potential participants. We also reached our planned sample size for in-depth interviews with clinicians. Unfortunately, our FGs with participants had to be curtailed because of the COVID-19 pandemic and data saturation was not achieved.

The clinician survey demonstrated a variety in practice and opinion. The parent survey suggested that women and their families generally preferred vaginal birth at later gestations and CS for preterm infants. The interactive workshop and Delphi consensus process confirmed the need for more evidence and, hence, the case for a trial. The Delphi consensus process provided rich information on what sort of trial could be conducted and how it could best be performed. It was agreed that any trial should address the areas with most uncertainty, including the management of women at 26–32 weeks' gestation with either spontaneous preterm labour (cephalic presentation) or where PTB was medically indicated.

Several other clear themes were identified and these are listed below:

- The challenges of the concept of equipoise for both participants and clinicians.
- Not all clinicians and not all potential participants are in equipoise about every clinical situation (despite the lack of formal evidence).
- There is a need for clinicians to have confidence in trial design, resources, the trial team and their clinical abilities to deliver both arms of any trial (e.g. performing vaginal breech deliveries).
- Clinicians would value the option of selecting their own inclusion and exclusion criteria (within a range offered by the trial) that are tailored to their own areas of equipoise.
- There is need for participants to be provided with information about the trial early on in the process (i.e. before labour).
- There is a need to tailor recruitment approaches for particular participants, including those from minority ethnic groups.
- Any trial in this area is likely to be 'challenging'.

Conclusions

Implications for health care

Evidence is lacking on the optimal MoB for the 60,000 babies born preterm in the UK each year. Both women and clinicians would like more evidence, but are conscious of the challenges inherent in recruiting to and participating in any trial.

Implications for research

A trial to determine the optimal MoB for women and babies at risk of PTB is urgently needed, but will be challenging to conduct. The outline and detailed design of CASSAVAplus, which we used to consult with potential participants and clinicians, provides a template that can be modified with feedback gained, after further systematic review and with consideration of a likely budget envelope. A study within a trial could be helpful in determining the most inclusive approach for involving pregnant women from ethnic minorities at risk of PTB. A pilot within any substantive trial, supported by qualitative methodology, could inform trial procedures, and an adaptive design might address the variety in participant characteristics.

Summary
There is broad agreement from parents and health-care professionals that a trial on the optimal MoB for preterm babies is needed. We conclude that a trial should be conducted and the challenges outlined resolved. The CASSAVA project has provided a strong basis on how to move forward and how such a trial could be carried out.

Trial registration

This trial is registered as ISRCTN12295730.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 61. See the NIHR Journals Library website for further project information.

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.014

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 17/22/02. The contractual start date was in November 2018. The draft report began editorial review in January 2021 and was accepted for publication in June 2021. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).