BMJ Open

PRECIOUS study (PREterm Caesarean/vaginal birth and IVH/OUtcomeS): does mode of birth reduce the risk of death or brain injury in very preterm babies? A cohort and emulated target trial protocol

David Odd ,[1] Nicola F Reeve ,[2] Jane Barnett,[3] Judith Cutter,[4] Rhian Daniel,[2] Chris Gale ,[5] Dimitris Siasakos[6]

To cite: Odd D, Reeve NF, Barnett J, *et al*. PRECIOUS study (PREterm Caesarean/vaginal birth and IVH/OUtcomeS): does mode of birth reduce the risk of death or brain injury in very preterm babies? A cohort and emulated target trial protocol. *BMJ Open* 2024;**14**:e089722. doi:10.1136/bmjopen-2024-089722

► Prepublication history for this paper is available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-089722).

Received 06 June 2024
Accepted 06 August 2024

[1]University Hospital of Wales, Cardiff, UK
[2]Cardiff University, Cardiff, UK
[3]Patient Representative, Cardiff, UK
[4]Cardiff and Vale University Health Board, Cardiff, UK
[5]Neonatal Medicine, School of Public Health, Imperial College London, London, UK
[6]UCL EGA Institute for Women's Health, UCL, London, UK

Correspondence to
Dr David Odd;
OddD@cardiff.ac.uk

ABSTRACT

Introduction Very preterm babies are at risk of poor neurodevelopmental outcomes and death. Intraventricular haemorrhage (IVH) after birth is the most prevalent cause of this. Birth by caesarean section may protect against IVH in very preterm babies, but the evidence is limited. The aim is to identify and obtain the quantitative evidence needed to inform a future definitive clinical trial to determine the optimal mode of delivery in preterm birth.

Methods and analysis We will use three broad workstreams (WS) to answer complementary questions. WSs 1 and 2 involve the analysis of routinely recorded national clinical data held in an established research database. In WS1 (October 2023–March 2024), we will use conventional methods to identify what is needed to undertake a trial: the population of interest, areas of equipoise and a plausible range of effect sizes. In WS2 (April 2024–October 2024), using an emulated target trial framework, we will attempt to make inferences about the treatment effect from such a future trial and will identify potential challenges in recruitment and estimate likely 'intention-to-treat' versus 'per-protocol' profiles; these analyses will also be useful for power calculations for future possible trials. In WS3 (October 2024–March 2025), we will convene a consensus meeting with key stakeholders, supported by a clinical trials unit, to develop a multicentre clinical trial to identify the optimal mode of birth for preterm deliveries.

Ethics and dissemination In this study, we will use deidentified data held in the National Neonatal Research Database (NNRD), an established national population database; parents can opt out of their baby's data being held in the NNRD. HRA/Health and Care Research Wales and National Health Service (NHS) study-specific Research Ethics Committee approval (London—Queen Square Research Ethics Committee) (Ref: 23/LO/0826) ethical approval has been obtained. Key outputs of the PRECIOUS (PREterm Caesarean/vaginal birth and IVH/OUtcomeS) study include the identification of the data, and accordingly of the multidisciplinary team required, to develop, gain funding and complete, a clinical trial to definitively identify the optimal mode of delivery for preterm infants and their mothers.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Data include all infants born alive and admitted to neonatal units in England and Wales.
⇒ Data have detailed measures of intrapartum care and neonatal outcomes.
⇒ Interpretation will be limited due to the exclusion of stillborn and labour ward deaths.
⇒ Causal inference and interpretation will be limited due to the use of routinely collected NHS data.

BACKGROUND

Expectant mothers report that the health of their baby is their single biggest priority,[1] yet there is insufficient evidence to guide many healthcare decisions.[2] Preterm babies are a group at high risk of poor neurodevelopmental outcomes and death,[3] and intraventricular haemorrhage (IVH) after birth is the most prevalent underlying cause of this.[4] IVH is a common complication in preterm babies and involves bleeding into the fluid spaces (ventricles) within the brain. IVHs are often graded from 1 to 4,[5] with grades 3 (where the blood distorts the ventricles) and 4 (additional damage to surrounding brain tissue) considered severe bleeds. Reducing IVH and other perinatal brain injury is a key part of the National Maternity Ambition[6] and while a small number of interventions may reduce the risk,[7–9] no effective treatment is available.[10–13]

Observational data suggest that birth by caesarean section (CS) may prevent IVH. Randomised trials in preterm babies to assess the impact of the mode of birth are limited, however, primarily due to recruitment difficulties.[14] A recent Cochrane systematic review[14] was unable to make recommendations due to insufficient data but concluded that a

definitive trial was feasible. Some observational studies have suggested that babies born by CS have lower risks of death and brain injury than those born vaginally. One study reported that babies born by CS had a substantially lower risk of severe IVH (2% vs 18%, p<0.001)[15] while another reported a 40% risk reduction,[16] compared with babies born vaginally. These associations persisted after adjustment for known confounders.[16] However, other work has been unable to confirm an association[17–20] and such conflicting observational evidence is insufficient to guide practice.[21]

Because of this uncertainty, a recent National Institute for Health Research (NIHR) funded project (CASSAVA) aimed to try and identify the patient population and clinical scenarios where a clinical trial to define the best mode of birth for preterm infants might be performed.[21] CASSAVA conducted clinician and patient surveys to clarify current practice and then performed consensus and Delphi workshops to help design and develop a protocol for a hypothetical clinical trial (CASSAVAplus trial). The project was able to achieve data saturation for most groups and achieved broad agreement between parents and professionals that a trial was needed. The parent survey suggested that women and their families preferred CS for more preterm births, but clinicians showed more variation in opinion across a range of scenarios.[21]

In agreement with other studies,[14] the CASSAVA study concluded that while trial on preterm mode of birth may be challenging, with an appropriate design and resourcing, the trial would be feasible—as have been previous trials of a mode of birth in term infants (Collea, 1980 #1370) (Gimovsky, 1983 #1368). CASSAVA proposed a trial with intentionally broad eligibility criteria, to allow clinicians to recruit where they had individual equipoise; and then to use an adaptive design to compensate once the trial was recruiting. This project—PRECIOUS (PREterm Caesarean/vaginal birth and IVH/OUtcomeS)—builds on CASSAVA and will provide the data necessary to inform a trial to identify optimal perinatal management of preterm births.

Emulated target trial framework

Whereas a well-designed and run Randomised Control Trial (RCT) is the gold standard for answering clinical questions,[22] such trials are not always feasible. Observational analyses can be used, and the results give (either implicitly or explicitly) a causal interpretation,[22] but such analyses may suffer from 'self-inflicted' bias, in addition to confounding. These biases stem from choices about which individuals to include, how exposure is ascertained, at what point individuals are 'recruited' to the study etc. The emulated target trial (ETT) framework aims to avoid these by aligning the design and analysis of the observational data as closely as possible to the design and analysis of a carefully defined target trial.[23] The methodology requires clear and transparent definitions, similar to that of a proposed RCT. These include clear eligibility criteria, and outcome measures, that mimic the target trial. Protocols, flow charts and data reporting for the emulated trial are then developed similarly to a real-world trial while being transparent on how the target trial may differ from any proposed RCT. Like all observational analyses aiming to estimate causal effects, appropriate control of confounders is key.

Aims

The overall aim of the PRECIOUS study is to identify the evidence needed to bridge the knowledge gap between the completed CASSAVA project and a future clinical trial to determine the optimal mode of delivery in preterm birth.

METHODS AND ANALYSIS

Three broad workstreams (WSs) will be used to answer complementary questions.

- WS1 (October 2023–March 2024): What is needed to undertake a trial: a retrospective cohort study to define with better precision the population of interest, areas of equipoise and range of potential effect sizes.
- WS2 (April 2024–October 2024): What is needed for a pragmatic, deliverable, future randomised control trial: development of emulated trial(s) to understand current deviation from intended treatments, cross-over, likely effect sizes and power.
- WS3 (October 2024–March 2025): Planning and development of the subsequent PRECIOUS+definitive trial.

Data source

WSs 1 and 2 will analyse data drawn from the National Neonatal Research Database (NNRD). The NNRD contains detailed data on all infants admitted to National Health Service (NHS) Neonatal Units in England and Wales. Neonatal units in England have contributed data since 2012, and all units in Wales since 2015. Data are extracted from point-of-care electronic health records during routine clinical care. A data extract, the Neonatal Data Set,[24] is checked for internal inconsistencies and duplicates.[25]

Population

All eligible infants, over an 11-year period across England (2012–2022) and a 7-year period across Wales (2015–2022) with data recorded in the NNRD.

Inclusion and exclusion

Inclusion

- Pregnancies where an infant was born between 22^{+0} and 31^{+6} weeks of gestation and admitted to a neonatal unit.

Exclusions

- Triplets or higher order multiple birth sets.

Primary outcome

- Death or survival with severe IVH before discharge from the neonatal unit, identified by routinely performed head ultrasound.

Secondary outcomes

- The majority of secondary outcomes will be aligned with the recently developed core outcome set for neonatal research[26]; survival to discharge, infection, necrotising enterocolitis, brain injury on imaging (all forms), retinopathy of prematurity and chronic lung disease.
- In addition, two additional outcomes have been identified by the Patient and Public Involvement (PPI) group; birth condition of the baby at birth (measured by the Apgar score) and length of neonatal unit admission.

Confounders and covariates

Factors a priori thought plausibly to be (1) associated with both the exposure (mode of birth) and the outcome, with (2) at least one of these associations being causal (to avoid collider bias) and (3) not affected by the exposure[27] will be considered as potential confounders.

- Gestational age at birth.
- Maternal comorbidities (pre-eclampsia, haemolytic anaemia, eclampsia, liver cholestasis of pregnancy, gestational diabetes mellitus, gestational hypertension, gestational proteinuria, antepartum haemorrhage, fetomaternal haemorrhage).
- Maternal receipt of antenatal steroids.
- Likely perinatal sepsis (maternal fever in labour >38°C, intrapartum antibiotics given, prolonged or prelabour Rupture of Membranes (ROM)).
- Parity.
- Spontaneous labour, induction or no labour.
- Presentation (cephalic vs other).
- Singleton or twin birth.
- Infant sex.
- Infant birth weight.
- Presence of prelabour or prolonged ruptured membranes.
- Mother's ethnicity.[28]
- Local Deprivation (Index of Multiple Deprivation (Quintiles)) (McLennan, 2019 #34).
- Maternal age.

WS1: what is needed to undertake a trial–a retrospective cohort study to define with better precision the population of interest, areas of equipoise and range of effect sizes

For this first set of analyses, the exposure allocation will be defined by the mode of delivery observed; either vaginal or CS.

Statistical analysis

Missing data in the exposure, outcome and covariates will be reported. The primary analyses will be performed on data multiply imputed using chained equations under an assumption of missing at random, with the default choices for the parametric form of each univariate imputation model inspected. Demographic and clinical characteristics of the cohorts will be described. We will inspect the distribution of mode of birth stratified by each covariate in turn. We will assess whether the relationships between each covariate and mode of birth are modified by core, a priori and identified factors (to be confirmed in ongoing PPI work, but likely to include gestational age, parity and twin-birth).

Next, we turn to the relationship between the observed mode of birth and the risk of the primary and secondary outcomes. The unadjusted association between mode of delivery and severe IVH will be summarised as a risk ratio; likewise the association between mode of delivery and each of the secondary outcomes. The main analysis for WS1 will be done using mixed effects logistic regression modelling to allow flexibility in investigating subgroups and possible interactions. Regression models will be fitted using severe IVH as the dependent variable. Initially, an unadjusted analysis will be performed, including a include a different random effect for each calendar year (to allow for changes in CS rate over the study period). A second model will be fitted after adjusting for the available confounders and covariates (above). The model will then be repeated for the other, secondary outcomes and a linear or negative binomial (depending on the model fit) regression model will be used to investigate the association between vaginal birth and the length of stay. Further analyses will be performed to identify if any relationship between mode of birth and IVH is modified by patient characteristics by fitting interaction terms to the model, and testing using the likelihood ratio test. Population impacts will be derived from the final modified model.

Finally, we will identify in which patient groups (eg, most extreme gestations) where the greatest variation in mode of birth is seen (reflecting lack of collective equipoise), and analyses will be repeated, restricting to this group. To assess the possible impact of non-resuscitation and labour ward deaths (with no corresponding neonatal admission) an additional analysis will be performed limited to infants of 26–31 weeks gestation where admission to neonatal services is highest,[4] and restricting the analysis to dyads where adequate time for either mode of delivery was likely feasible (defined as having received a complete course of antenatal steroids). Some covariates will be recoded to aid interpretation and implementation where commonly categorised in clinical practice (maternal age (coded as less/older than 40 years old), maternal comorbidities (yes/no), parity (primiparous or not), presentation (cephalic or other), ethnicity (white or other)), birth weight (below 10th centile, 10th–90th centile, above 90th centile)).

WS2: what is needed for a pragmatic, deliverable, future randomised control trial–analysis of emulated trial to understand profile, likely effect sizes and deviations from the intended (randomised) treatment

For this second set of analyses, an attempt will be made to ascertain, where possible, what the intended mode of birth was. Intended exposure will be defined as:

1. Vaginal: induction of labour is attempted (irrespective of the ultimate mode of birth) or spontaneous-onset preterm labour continues to a vaginal birth.
2. Caesarean: whenever the baby is born by CS without preceding induction of labour or deliveries where there was a decision to deliver an infant by CS in a woman presenting with spontaneous preterm labour.

The primary analysis will be repeated using the observed Mode of Birth (MoB) (ie, the exposure used in WS1).

ETT methods

From the results of WS1, a proposed eligible trial population (gestational age range, etc) will be derived, alongside other constraints commonly used to include/exclude trial participants.

Inclusion criteria

- Where one mode of birth or another is known to be contraindicated, or, from WS1, so rarely performed that this appears practically so (absolute cut-off to be defined at WS1 alongside PPI input).

Exclusions

- Maternal or fetal indications for CS.
- Antenatal diagnoseable congenital abnormalities.

A Consolidated Standards of Reporting Trials (CONSORT) compliant protocol and flow chart will be derived in order to identify the proposed eligible patients, based on a target population (above), modified by the additional information on effect sizes, areas of equipoise and target patient populations derived in WS1. The analysis will also be repeated using the whole population without modifications.

Confounders

Measured confounding will be dealt with using inverse probability weighting; that is, first a logistic regression model will be fitted with an intended mode of birth as the outcome (coded CS=1, VB=0) and all potential confounders as predictors. Those in the intended CS group will receive a weight of 1 divided by their estimated propensity score, and those in the intended VB group will receive a weight of 1 divided by (1 minus their estimated propensity score).

Statistical analysis

The treatment policy estimand (treatment, population, variable, population-level summary and handling of intercurrent events) will be estimated via an IP-weighted comparison of outcomes among individuals assigned to each mode of birth. These results will be used in sample size/power calculations for a future trial. Sensitivity analyses will interrogate the likely real-world role of a future RCT by testing the impact of increased/decreased cross-over between arms and limiting the population to those with the greatest variation in practice or to those with the proposed highest effect size (both identified in WS1).

WS3: planning and development of the PRECIOUS+trial

Finally, we will collate the results and convene a consensus meeting to move forward with the development of the PRECIOUS+trial. Invites will be extended to experts (including families) needed to successfully develop the subsequent trial including the PRECIOUS applicants, the Programme Advisory Group members, national and local stakeholders, patient/public representatives, a clinical trials unit and other academics (such as health economists and independent triallists).

Power and precision

The CASSAVA-Plus trial proposed to recruit enough women for analysis of 1100 women in each group, with a predicted incidence of death or severe IVH of 20% in the vaginal birth (VB) group and 15% in the CS group. We predict 57.3% of infants (less than 32 weeks gestation) will be born by CS while 42.7% by VB.[16] If we see similar outcomes and frequencies as above, with a population of 7753 very preterm births a year, over 11 years (using just English data)[29] we would have an estimated >99% power given the predicted sample size; and adequate power to test for subgroup and sensitivity analysis (eg, 90% power to detect the same difference in an isolated subgroup containing only 2549 infants (less than 3% of the population available to us)). All estimates assume a two-tailed alpha of 0.05).

Parent, patient and public involvement

This study was commissioned by Health and Care Research Wales (HCRW). An author of this protocol and study coinvestigator (JB) joins the project as PPI lead and parent input from a diverse PPI panel has been involved in planning and designing the study, specifically in the selection of study outcomes. Further PPI work is integrated into the project.

ETHICS AND DISSEMINATION

No patient-identifiable information will be used in this study and only existing anonymised data held in the NNRD will be used. HRA/HCRW and NHS study-specific Research Ethics Committee approval (London - Queen Square Research Ethics Committee) (Ref: 23/LO/0826) ethical approval has been obtained. Approval for inclusion of the data in this study was obtained from all English and Welsh neonatal units (the UK Neonatal Collaborative). The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions. Results will

be presented at national and international academic conferences and published in peer-reviewed scientific publications and parent-centred information will be dissemination through social media and online.

The PRECIOUS study aims to bridge the knowledge gap between the CASSAVA project and a future clinical trial investigating the optimal mode of birth for preterm infants. Using a combination of conventional regression analysis and ETT framework, we will determine the necessary information for conducting the trial, including the population of interest, areas of equipoise and relevant effect sizes that matter to both parents and clinicians, and clarify the requirements for a successful future randomised control trial, taking into account treatment deviations, cross-over and expected effect sizes. We will use this information to initiate the planning and further development of the future clinical trial, referred to as the PRECIOUS+trial.

X Chris Gale @DrCGale

Contributors DO, JC, RD, CG and DS conceived the study; DO, NFR, JB, JC, RD, CG and DS contributed to designing the study, developing the protocol for the study and this manuscript. DO, NFR, JB, JC, RD, CG and DS read and approved the final manuscript. DO is the guarantor of this work.

Funding This work was supported by Health and Care Research Wales (HCRW) grant number HRG-22-1935.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

ORCID iDs
David Odd http://orcid.org/0000-0002-6416-4966
Nicola F Reeve http://orcid.org/0000-0001-9602-6675
Chris Gale http://orcid.org/0000-0003-0707-876X

REFERENCES

1 Kingdon C, Neilson J, Singleton V, *et al*. Choice and birth method: mixed-method study of caesarean delivery for maternal request. *BJOG* 2009;116:886–95.
2 Preterm labour and birth nice guideline [NG25]. 2019.
3 Marlow N, Bennett C, Draper ES, *et al*. Perinatal outcomes for extremely preterm babies in relation to place of birth in England: the EPICure 2 study. *Arch Dis Child Fetal Neonatal Ed* 2014;99:F181–8.
4 Odd D, Williams T, Stoianova S, *et al*. The contribution of newborn health to child mortality across England. National Child Mortality Database (NCMD); 2022.
5 Papile LA, Burstein J, Burstein R, *et al*. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr* 1978;92:529–34.
6 Gale C, Ougham K, Jawad S, *et al*. Brain injury occurring during or soon after birth: annual incidence and rates of brain injuries to monitor progress against the national maternity ambition 2018 and 2019 national data. n.d. Available: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/662974/Report
7 Smit E, Odd D, Whitelaw A. Postnatal phenobarbital for the prevention of intraventricular haemorrhage in preterm infants. *Cochrane Database Syst Rev* 2013;2013:CD001691CD001691.
8 Liu J, Wang Q, Zhao J, *et al*. The combined antenatal corticosteroids and vitamin K therapy for preventing periventricular-intraventricular hemorrhage in premature newborns less than 35 weeks gestation. *J Trop Pediatr* 2006;52:355–9.
6 Yao SL, Smit E, Odd D. The effectiveness of interventions to prevent intraventricular haemorrhage in premature infants: A systematic review and network meta-analysis. *NPM* 2022;16:5–20.
10 Luyt K, Jary S, Lea C, *et al*. Ten-year follow-up of a randomised trial of drainage, irrigation and fibrinolytic therapy (DRIFT) in infants with post-haemorrhagic ventricular dilatation. *Health Technol Assess* 2019;23:1–116.
11 Cizmeci MN, Groenendaal F, Liem KD, *et al*. Randomized Controlled Early versus Late Ventricular Intervention Study in Posthemorrhagic Ventricular Dilatation: Outcome at 2 Years. *J Pediatr* 2020;226:28–35.
12 Mahoney L, Luyt K, Harding D, *et al*. Treatment for Post-hemorrhagic Ventricular Dilatation: A Multiple-Treatment Meta-Analysis. *Front Pediatr* 2020;8:238.
13 Nice. IPG412 drainage, irrigation and fibrinolytic therapy (drift) for post-haemorrhagic hydrocephalus in preterm infants: guidance. 2011.
14 Alfirevic Z, Milan SJ, Livio S. Caesarean section versus vaginal delivery for preterm birth in singletons. *Cochrane Database Syst Rev* 2012;6:CD000078.
15 Dani C, Poggi C, Bertini G, *et al*. Method of delivery and intraventricular haemorrhage in extremely preterm infants. *J Matern Fetal Neonatal Med* 2010;23:1419–23.
16 Gamaleldin I, Harding D, Siassakos D, *et al*. Significant intraventricular hemorrhage is more likely in very preterm infants born by vaginal delivery: a multi-centre retrospective cohort study. *J Matern Fetal Neonatal Med* 2019;32:477–82.
17 Linder N, Hiersch L, Fridman E, *et al*. The effect of gestational age on neonatal outcome in low-risk singleton term deliveries. *J Matern Fetal Neonatal Med* 2015;28:297–302.
18 Ljustina S, Berisavac I, Berisavac M, *et al*. Analysis of intracranial hemorrhage grade in preterm singleton pregnancies delivered vaginally or by cesarean section. *VSP* 2013;70:255–8.
19 Durie DE, Sciscione AC, Hoffman MK, *et al*. Mode of delivery and outcomes in very low-birth-weight infants in the vertex presentation. *Am J Perinatol* 2011;28:195–200.
20 Barzilay E, Gadot Y, Koren G. Safety of vaginal delivery in very low birthweight vertex singletons: a meta-analysis. *J Matern Fetal Neonatal Med* 2016;29:3724–9.
21 Norman J-O, Lawton J-O, Stock S-O, *et al*. n.d. Feasibility and design of a trial regarding the optimal mode of delivery for preterm birth: the CASSAVA multiple methods study. :(2046-4924 (Electronic)).
22 Lawlor DA, Davey Smith G, Ebrahim S. Commentary: The hormone replacement-coronary heart disease conundrum: is this the death of observational epidemiology? *Int J Epidemiol* 2004;33:464–7.
23 Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. *Am J Epidemiol* 2016;183:758–64.
24 Digital N. DAPB1595: neonatal data set. 2022.
25 Gale C, Morris I. The UK National Neonatal Research Database: using neonatal data for research, quality improvement and more. *Arch Dis Child Educ Pract Ed* 2016;101:216–8.
26 Webbe JWH, Duffy JMN, Afonso E, *et al*. Core outcomes in neonatology: development of a core outcome set for neonatal research. *Arch Dis Child Fetal Neonatal Ed* 2020;105:425–31.
27 McNamee R. Confounding and confounders. *Occup Environ Med* 2003;60:227–34.
28 Office for National Statistics (UK). Ethnicity and national identity in England and Wales: 2011. 2012. Available: https://www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/ethnicity/articles/ethnicityandnationalidentityinenglandandwales/2012-12-11
29 Gale C, Ougham K, Jawad S, *et al*. Brain injury occurring during or soon after birth: annual incidence and rates of brain injuries to monitor progress against the national maternity ambition 2018 and 2019 national data. Neonatal Data Analysis Unit, Imperial College London; 2021. Available: https://www.imperial.ac.uk/media/imperial-college/medicine/dept-medicine/infectious-diseases/neonatology/2018-2019-Brain-injury-occurring-during-or-soon-after-birth-NATIONAL-DATA-280121.pdf