TRANSFER

ThReatened preterm birth, Assessment of the Need for in utero tranSFER between 22+0-23+6 weeks' gestation.

Protocol

Version 3.0 (28-Oct-21)

PROTOCOL CHANGES		
Date of change	**Protocol version number**	**Summary of Change**
06-May-2021	V2.0	• Clarification to Eligibility criteria (section 10.1), Patient inclusion (section 10.3), and Data collection (section 11.1) • Clarification to study type • Minor changes relating to typographical errors
28-Oct-2021	V3.0	• Updated with the new end date for patient inclusion (section 2 and section 9) • The word 'study' has been removed from the body of the document to reflect the fact that TRANSFER is not deemed to be Research according to the NHS Decision Tool.

Full Title:

Assessing the incidence of threatened preterm birth in women presenting at 22+0-23+6 weeks' gestation, a service evaluation to inform the need for in utero transfer.

Short project title/acronym:

TRANSFER

In utero transfer 22-23+6 weeks' gestation for threatened preterm birth

Protocol version number and date
2.0; 06-May 2021

Signatures

The undersigned confirm that the following protocol has been agreed and accepted.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation.
I also confirm that I will make the findings of the project publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the project will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Study Lead: Dr Melanie Joanne Griffin

Signature: Date: 15/03/2021

Contents

1. Study Management Group

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2. Project summary

Study Title: Assessing the incidence of threatened preterm birth in women presenting at 22+0-23+6 weeks' gestation, a service evaluation to inform the need for in utero transfer.

Short title: TRANSFER

ThReatened preterm birth, Assessment of the Need for in utero tranSFER between 22+0-23+6 weeks' gestation.

Project Design: Multicentre prospective service evaluation

Project duration: 12 months

Project Participants: All pregnant women presenting between 22+0-23+6 weeks gestation, requiring transfer to a maternity unit with co-located neonatal intensive care unit (level 3)

Planned Size of enrolment target: Rolling enrolment during ten month study patient inclusion window

Follow up duration: Until delivery

Planned Project Period: 20 weeks after ten month study enrolment duration

Study Question/Aim(s): To establish the incidence of women presenting with threatened preterm birth to obstetric units in England, Scotland, Wales and Northern Ireland between 22+0-23+6 weeks' gestation and determine the number requiring transfer to an obstetric unit with co-located neonatal intensive care unit (NICU) (level 3).

Funding and support in kind

The costs of running the project have been supported by The South West Neonatal Operational Delivery Network and the Bristol LMS

The project will be coordinated via the Birmingham Centre for Observational and Prospective Studies (BiCOPS) at the University of Birmingham.

The project has been designed by Dr Melanie Griffin and Dr Victoria Hodgetts-Morton with input from Professor Katie Morris and Dr Adam Smith-Collins.

Protocol contributors

This protocol has been developed by the study management group, with support from BiCOPS.

3. KEY WORDS: pregnancy, preterm birth, NICU, transfer, in utero

4. Background

Preterm birth is a significant problem with 8-9% babies born preterm across the U.K (1, 2). The majority of these early births occur in women presenting beyond 27 weeks' gestation. Infants born before 27 weeks gestation require highly specialized care and are at significant risk of death or disability(3). In 2019 the British Association of Perinatal Medicine (BAPM) published their updated framework "Perinatal Management of Extreme Preterm Birth Before 27 weeks of Gestation". Of particular note is the risk-based approach to decisions about care pathways following delivery for the most extremely preterm infants born between 22+0 and 23+6 weeks. Babies at moderate risk of death or severe disability should receive active treatment; those at extremely high risk would normally be managed palliatively, whilst those babies at high risk should be managed in line with parental wishes following careful counselling.

However, the number of women presenting at risk of delivery between 22 and 24 weeks is unknown.

5. Rationale

Previous guidance around provision of active care in the most extreme preterm infants (Critical care decisions in fetal and neonatal medicine, Nuffield Council on Bioethics, 2006) meant that active care was very rarely considered for infants 22+0-22+6 weeks' gestation, and uncommonly for those 23+0-23+6 weeks' gestation. Improved outcomes for the most extreme preterm infants, reflected in the new guidance, means more infants will be offered active care(4). Neonatal outcomes are substantially better for extreme preterm infants who are delivered in a maternity setting, which is co-located with a tertiary neonatal intensive care unit (NICU). Therefore, optimal care for those infants on an active care pathway includes the need to ensure antenatal transfer of women with threatened preterm delivery who present in a unit without a NICU. This change means that there will be increased demand for both maternity and neonatal capacity in tertiary settings. Whilst there is national data on the number of infants at these gestations surviving delivery and

being admitted to neonatal units, this does not adequately capture the impact on maternity services. The limited and incomplete information regarding the number of women within this gestational age group who need to be transferred to optimise place of birth, results in challenges to service provision and planning. This service evaluation has been designed to answer these important questions.

6. Project question and aims

6.1 Objectives

The main aim of this project is to establish the incidence of women presenting with threatened preterm birth to obstetric units in England, Wales, Scotland and Northern Ireland between 22+0-23+6 weeks' gestation and determine the number requiring transfer to an obstetric unit with co-located neonatal intensive care unit (level 3).

The specific objectives are to:

1. Calculate the incidence of women presenting with threatened preterm birth (TPTB) to obstetric units in England, Wales, Scotland and Northern Ireland between 22+0-23+6 weeks' gestation.
2. Determine the number of women who present outside an obstetric unit with a NICU.
3. Determine the number of in utero transfers of women presenting between 22+0 -23+6 weeks' gestation
4. Determine the number of women who deliver between 22+0 -23+6 weeks' gestation in a unit without a NICU.

6.2 Outcomes

The following data will be recorded for each presentation with threatened preterm birth between 22+0-23+6 weeks' gestation:

- Gestation in completed weeks and days (including estimated date of delivery)
- Presence of a co-located NICU (level 3) unit at presenting site
- Measurement of biomarker predicting risk of preterm birth (fetal fibronectin or phosphorylated IGFBP-1 protein (actim ® partus)
- Need for transfer to unit with co-located NICU (level 3)
- Length of antenatal hospital stay, both in presenting unit and receiving unit.
- Delivery in receiving unit during the hospital episode transfer occurred in
- Gestation at delivery (in completed weeks and days)
- Survival to admission to NICU
- Pregnancy outcome; miscarriage, live birth, stillbirth

7. Project design

This is a national, multi-centre, prospective, service evaluation. There are no project interventions and only anonymised routinely collected data will be included.

8. Project setting

All obstetric units in England, Scotland, Wales and Northern Ireland are eligible to participate in the study. Initially, the network of 75 obstetric units throughout England, Scotland, Wales and Northern Ireland, participating in the CSTICH studies will be invited.

By the involvement of both large tertiary centres and small district general hospitals, we aim to include a diverse population and increase the wider utility of this work.

There will be a dedicated site lead in each centre, who is responsible for identifying appropriate cases and coordinating data collection.

9. Project period

Ideally, all sites will capture data on all eligible women presenting to their unit as soon as they are set up to take part in TRANSFER and continue until 31-Mar-22.

The project start date is 17-May-2021. For 10 months from this date, data on all eligible women **(pregnant women ≥16 years old admitted to an obstetric unit with threatened preterm birth between 22+0-23+6 weeks' gestation**), will be recorded prospectively.

All women will be followed up until delivery.

Key dates	Milestone
15-Mar-2021	Protocol release. Site registration open.
17-May-2021	Data collection period starts. Participant identification begins.
31-Mar-2022	Participant identification ends.
Follow-up period: 20 weeks from inclusion into TRANSFER	

TRANSFER has rolling registration so hospital can sign up to participate after the launch date of 17-May-2021.

10. Participant inclusion

10.1 Eligibility criteria

Pregnant women ≥16 years old admitted to an obstetric unit with threatened preterm birth between 22+0-23+6 weeks' gestation.

Note: If the receiving hospital deems the patient ineligible, but the presenting centre assessed the woman as eligible for the TRANSFER project, the patient should still be included and the data collected. This will help to ensure each patient has a full set of data.

Threatened preterm birth is defined as: Any woman presenting with regular uterine activity but no cervical change and/or ruptured membranes and/or vaginal bleeding who in the opinion of the assessing medical team is in threatened preterm birth.

10.2 Recruitment target

Given the aim of this project is to calculate the incidence of threatened preterm birth requiring in utero transfer during this gestational window a pragmatic approach has been taken with rolling patient inclusion during this ten-month period.

At least 80% of all women presenting to participating hospitals between 22+0-23+6 weeks' gestation with threatened preterm birth during the study period.

10.3 Patient identification

Each site will have a local method of identifying women presenting with threatened preterm birth within the specified gestational window.

This includes notifying the site lead when regional units are contacted to discuss care pathways and possible transfer by the unit at which the woman presents.

Data should be reported for all women in whom the clinical team believe there is a realistic risk of preterm delivery within the gestational window. This includes cases where there is a decision (from clinicians or families) not to pursue an active care pathway, where preterm delivery occurs prior to potential transfer or where

presentation occurs within a tertiary setting and therefore transfer is not indicated, in addition to those cases where antenatal transfer does occur.

11. Data collection

11.1 Data collection at participating sites

The site lead at each centre should identify a team to:

- Ensure senior midwifery staff and medical staff working on central delivery suite are aware of this project and contact details for local project team.
- Identify women presenting at your unit with threatened preterm birth within the gestational window
- Identify women who were transferred to your unit because they were assessed as being in threatened preterm birth within the gestational window by the presenting hospital
- Weekly monitor the participants to ensure completion of follow-up data

11.2 Baseline data

Baseline data will be recorded at the index admission following confirmation of eligibility. Consultant obstetricians, research fellows, obstetrics trainees or research midwives, will collect data.

Electronic case report forms (eCRFs) will be used by the clinical care team to capture data.

Only routine data will be collected, no additional information will be sought, as this is a record of practice only.

12. Data Handling and Record Keeping

12.1 Data Management

Data will be collected at the time of project entry and at time of delivery.

Data will be collected and stored online through a secure server running the Research Electronic Data Capture (REDCap) web application. REDCap is a secure, web-based software platform designed to support data capture of single and multi-site studies. Data will be entered directly onto the REDCap database by project collaborators at participating hospitals sites.

Site study collaborators will be provided with a paper copy of the eCRF to facilitate data collection. If this is used, they should then transfer data from the paper CRF to the online REDCap database located at https://www.bistc.redcap.bham.ac.uk. BiCOPS data management staff will check all incoming data CRFs for completeness, data consistency and compliance with the protocol. If discrepancies or missing data are identified, the data management staff will raise queries with the study team at the participating hospital.

The linkage between REDCap ID and participants will be maintained in strict confidence at participating sites. This data will not be submitted to the study office and will not be sent outside of the participating site.

12.2 Missing Data

The online database has been designed to allow sites to securely access an individual patient's data for all CRFs throughout the study period. This means that any missing or erroneous data can be amended by the local investigators whilst the data collection period is ongoing. In order to maximise data completion and emphasise its importance to collaborators, participating centres with > 5% missing data in mandatory fields (i.e. < 95% data completeness) will be excluded from the project.

12.3 Data Security and Data Protection

The security of the project database system is governed by the policies of the University of Birmingham. The project database will be hosted on the University's REDCap system managed and maintained by the BiCOPS team.

Data management and data security within the BiCOPS will abide by the requirements of the General Data Protection Regulations (GDPR) and any subsequent amendments. The project will be conducted at collaborating sites in accordance with the country-specific data protection requirements. Data will be acquired and stored on the REDCap platform. Access to data will be restricted; each individual collaborator entering data for TRANSFER will have their own username and password. Each participant will be allocated a unique project number at entry. All communication will use this as the identifier. All data will be analysed and reported in summary format. No individual will be identifiable.

13. Statistical analyses

13.1 The planned analyses are:

- Calculation of the incidence of women presenting with threatened preterm birth to obstetric units in England, Wales, Scotland and Northern Ireland between 22+0-23+6 weeks gestation
- Recording the number of women who present outside a maternity unit with a NICU
- Determining the number of in utero transfers of women presenting between 22+0 -23+6 weeks' gestation with threatened preterm birth
- Determining the number of women who deliver between 22+0 -23+6 weeks gestation that deliver in a unit without a NICU and not transferred
- There is no planned repeat analysis or subgroup analysis. Episodes with missing data will be excluded from analysis. Where possible statistical

methods including imputation will be used in order to account for missing data

- All analysis will be completed in SPSS (version 26, IBM).

14. Confidentiality

Patient identifiable information will not be collected in this project. All participant data held at the University of Birmingham will be anonymised.

All data collected about participants will be identified using only a unique project number (REDCap record ID). This number will be automatically allocated via REDCap once a new patient record is created in the database.

Any correspondence between the project office and hospital sites will use the project number only.

The linkage between REDCap record ID and participants will be maintained in strict confidence at participating sites. This data will not be submitted to the study office and will not be sent outside of the participating site.

Confidentiality of all participants' data will be maintained and there will be no disclosure of information by which participants may be identified to any third party other than those directly involved in the treatment of the participant. The participants will not by identifiable with regards to any future publications relating to this project.

15. Regulatory Approval

In the UK, this project is categorised as a service evaluation, not research (see Appendix 1 for the HRA decision tool outcome). Therefore, sites may participate once local clinical approval is in place.

The site lead at each participating site is responsible for obtaining necessary local approval. Collaborators will be required to confirm that approval is in place prior to the start of the project at their site.

Only routinely collected data will be collected in this project. Patients will not undergo any additional investigations or clinical follow-up for the study. No sensitive or identifiable data will be collected on the REDCap database; the patient's clinical team will upload anonymised data only.

16. Project Administration

The project has been developed by the study management group (SMG). This study management group is chaired by the Project Lead and includes other clinical collaborators plus methodologists and the study management lead.

The project will be under the auspices of the Project Lead and the Birmingham Centre for Observational and Prospective Studies.

16.1 Local Study Teams

A local site lead should be identified at each participating centre. They will work with the local team to ensure that a pathway is in place to identify eligible patients and ensure collection and completion of outcome data.

Where feasible, the use of trainee collaboratives will be encouraged to aid in the delivery of this project. Trainees may:

- Facilitate delivery at site
- Liaise with the SMG as necessary
- Ensure appropriate local staff resources are maintained (cover provided for absence) to deliver the study

17. Patient and Public Development

We have engaged with the British Association of Perinatal Medicine (BAPM), UK Preterm Clinical Network (UKPCN) and regional Operational Delivery Network Leads in Neonatal Critical Care in writing this protocol.

18. Publication Policy

The project Lead will co-ordinate dissemination of data from this service evaluation. All publications using data from this project to undertake original analyses will be submitted to the SMG for review before release. The success of the project depends on many clinicians. For this reason, credit for the results will not be given to the committees or central organisers, but to all who have collaborated and participated in the TRANSFER. Acknowledgement will include all collaborators, members of the project committees, the SMG and administrative staff. Authorship at the head of the primary results paper will be cited as a collaborative group to avoid giving undue prominence to any individual. All contributors to the project will be listed at the end of the report, with their contribution to the project identified.

18.1 Dissemination of Findings

The results of this service evaluation will be submitted for publication in a peer reviewed scientific journal and the results will also be presented at meetings both national and international.

No centre's individual data will be shared with other centres and national data will be presented in an amalgamated format where no individual trust's performance will be visible.

19. Finance and Funding

The project will be coordinated via Birmingham Centre for Observational and Prospective Studies. Participating centres will not bear any costs for being part of this service evaluation. Similarly, no financial reimbursement will be made to units or investigators for their involvement.

20. References

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2. Wagijo M-a, Sheikh A, Duijts L, Been JV. Reducing tobacco smoking and smoke exposure to prevent preterm birth and its complications. Paediatric Respiratory Reviews. 2017;22:3-10.
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4. Costeloe KL, Hennessy EM, Haider S, Stacey F, Marlow N, Draper ES. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). Bmj. 2012;345:e7976.
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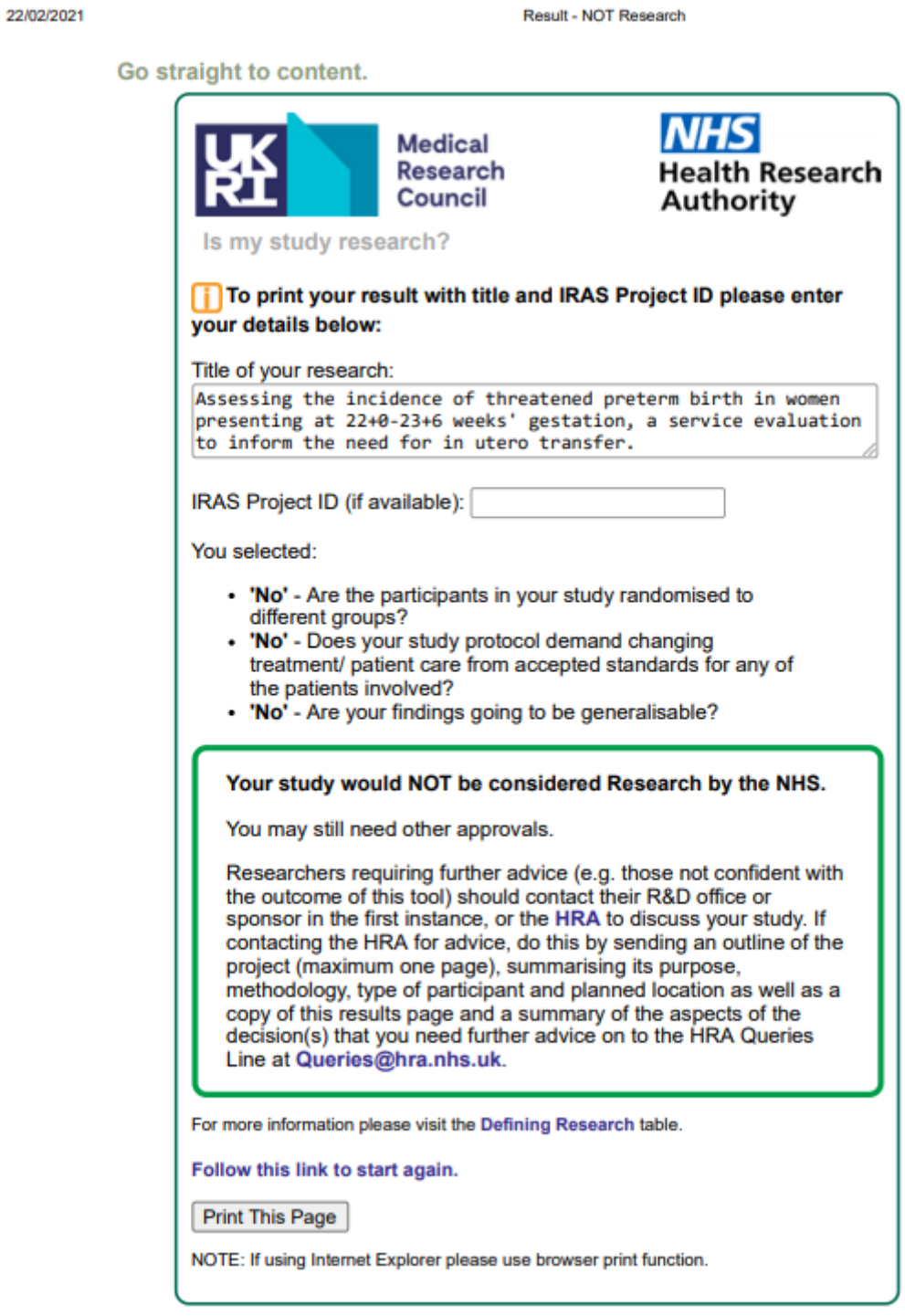
6. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. Journal of Biomedical Informatics. 2009;42(2):377-81.

20. APPENDIX 1: HRA Decision Tool



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- **'No'** - Does your study protocol demand changing treatment/ patient care from accepted standards for any of the patients involved?
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