TRIAL PROTOCOL

C-STICH2: Emergency Cervical Cerclage to Prevent Miscarriage and Preterm Birth - a Randomised Controlled Trial

Version Number: **4.0**

Version Date: 17th September 2020

PROTOCOL AMENDMENTS

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
2	**31st January 2020**	**3.0**	**Substantial**	**Change to qualitative study consent processes and introduction of letters to contact women about the qualitative study.**
3	**31st July 2020**	**3.1**	**Substantial**	**Addition of a consented observational cohort to run alongside the randomised controlled trial.**

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PROTOCOL SIGN OFF

CI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol.

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 clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

This protocol has been approved by:

Trial Name: Protocol Version Number:	C-STICH2 Version: 4.0
Protocol Version Date:	17th September 2020
CI Name:	R. Katie Morris
Trial Role:	Chief Investigator
Signature and date:	 17/09/2020

Sponsor statement:

By signing the IRAS form for this trial, Birmingham Women's and Children's NHS Foundation Trust, acting as Sponsor of this trial, confirm approval of this protocol.

Reference Numbers	
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PI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the trial in compliance with the approved protocol.

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 clinical investigation without the prior written consent of the Sponsor.

This protocol has been approved by:

Trial Name:	C-STICH2
Protocol Version Number:	Version: __ __
Protocol Version Date:	__ __ / __ __ / __ __ __ __
PI Name:	
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Trial Facebook (TBC)	@C_STICH2

ABBREVIATIONS

Abbreviation	Term
BCTU	Birmingham Clinical Trials Unit
BWCH	Birmingham Women's and Children's Hospital
BWCNFT	Birmingham Women's and Children's NHS Foundation Trust
CiG	Co-investigator Group
CRF	Case Report Form
DCF	Data Clarification Form
DMC	Data Monitoring Committee
ECC	Emergency Cervical Cerclage
HCP	Healthcare Professional
HVS	High Vaginal Swab
ICF	Informed Consent Form
ISF	Investigators Site File
MOA	Major Outcomes Averted
PARCA-R	Parent Report of Children's Abilities - Revised for preterm infants
PIS	Participant Information Sheet
PPROM	Preterm pre-labour rupture of membranes
PSS	Personal Social Services
PTB	Preterm Birth
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAP	Statistical Analysis Plan
TMF	Trial Master File
TMG	Trial Management Group

UoB	University of Birmingham

DEFINITIONS

Term	Abbreviation	Description
Adverse Event	AE	Any untoward medical occurrence in a participant or clinical trial subject participating in the trial which does not necessarily have a causal relationship with the intervention received.
Birmingham Clinical Trials Unit	BCTU	The co-ordinating centre for the trial.
Policies	POL	Policies are developed to describe the approach of the University of Birmingham (UoB) on areas that heavily regulated. Policies may also be developed when there is ambiguity in how regulatory requirements should be implemented in the QMS or when procedures to be captured in the QMS address areas controversial within the UoB at the time of implementation. Policies explain why the UoB has its procedures, especially when they seem to deviate from the regulatory requirements. Policies should be read in conjunction with the relevant SOP. Policies that are not part of a Quality Manual are coded up as 'POL'.
Quality Control Documents	QCD	Quality Control Documents can be instructions, forms,

		templates or checklists. They are developed to share best practices, promote standardisation to guarantee quality standards are maintained and reduce resources otherwise needed to develop similar documents. Unless indicated otherwise in the relevant SOP, QCDs are not mandatory and are designed to be an optional aid to UoB staff.
Quality Management System	QMS	A Quality Management System (QMS) is a system that includes procedures and policies to describe how certain tasks should be performed and that encapsulate any standards and/or regulatory requirements that may apply to those tasks. By adhering to the Quality Management System, the user and the UoB will be assured that applicable regulations are adhered to.
Related Event		An event which resulted from the administration of any of the research procedures.
Serious Adverse Event	SAE	An untoward occurrence that: • Results in death • Is life-threatening* • Requires hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly/ birth defect

		• Or is otherwise considered medically significant by the Investigator**
Source data		All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial
Standard Operating Procedures	SOP	Standard Operating Procedures are detailed written instructions to achieve uniformity in the performance of a specific function. They define tasks, allocate responsibilities, detail processes, indicate documents and templates to be used and cross-reference to other work instructions and guidance or policy documents. They are standards to which the UoB may be audited or inspected.
Unexpected and Related Event		An event which meets the definition of both an Unexpected Event and a Related Event
Unexpected Event		The type of event that is not listed in the protocol as an expected occurrence.

TRIAL SUMMARY

Title

C-STICH2: Emergency Cervical Cerclage to Prevent Miscarriage and Preterm Birth - a Randomised Controlled Trial

Objectives

- To determine if an emergency cervical cerclage (ECC) reduces pregnancy loss (miscarriage, termination of pregnancy, stillbirth or neonatal death within 7 days of delivery) in women who present with cervical dilatation sufficient toallow exposure of the unruptured, fetal membranes at or below the level of the external os between 16+0 and 27+6 weeks.
- To follow up all surviving babies to 2 years of age to determine general health and medium term neurodevelopmental outcomes.
- To determine the complication rates at ECC:
    - Including the number of women who suffer iatrogenic rupture of membranes during the procedure.
    - The rate of insertion failure in women allocated to have an ECC inserted.
    - To explore predictors of successful ECC placement such as magnitude of dilatation.

Trial Design

A randomised controlled, multicentre trial (RCT) with an internal pilot, a nested qualitative process evaluation and cost-effectiveness analysis. Following the internal pilot and nested qualitative evaluation a prospective observational cohort study was developed to run alongside the RCT.

Participant Population and Sample Size for RCT

Pregnant women presenting at 16+0 - 27+6 weeks, with premature cervical dilatation and exposed, unruptured fetal membranes will be invited to take part in a RCT of ECC vs no cervical cerclage.

Setting: Maternity units within the UK.

Sample size: up to 260 women.

Eligibility Criteria for RCT

Inclusion Criteria:

- Women 16 years of age or older
- Cervical dilatation sufficient to allow exposure of the unruptured, fetal membranes at or below the level of the external os

- Singleton pregnancy
- Gestational age 16+0 to 27+6 weeks
- Able to give informed written consent.

Exclusion Criteria:

- Contraindication to emergency cerclage as judged by the clinician
- Cervical cerclage (vaginal or abdominal) inserted earlier in this pregnancy or in a previous pregnancy that remains in situ.
- Gestational age <16+0 weeks
- Gestional age ≥ 28+0 weeks
- Unable to give informed consent

Interventions

Health technology being assessed: ECC +/- other usual adjuncts (e.g. progesterone/antibiotics/tocolytics) will be compared with no ECC +/- other usual adjuncts. The other adjuncts will be at the discretion of the clinical team caring for the women.

Outcome Measures

Primary obstetric outcome: Pregnancy loss (defined as miscarriage, termination of pregnancy, stillbirth or neonatal death within 7 days of birth).

Secondary outcomes: Maternal and fetal health outcomes which includes the core outcome set for preterm birth, all 13 outcomes [1].

Two-year outcomes - Assessment of developmental attainment using the Parent Report of Children's Abilities - Revised for preterm infants (PARCA-R). Parent questionnaires to collect data on specific diagnoses at 2 years e.g. cerebral palsy.

Cost effectiveness evaluation: At birth and two years of age.

Observational Cohort

Consented observational cohort added following pilot review. This will supplement effectiveness evaluation. The inclusion and exclusion criteria for the cohort remains the same as the RCT. All outcome measures collected in the RCT will be collected in the observational cohort including the two year outcomes.

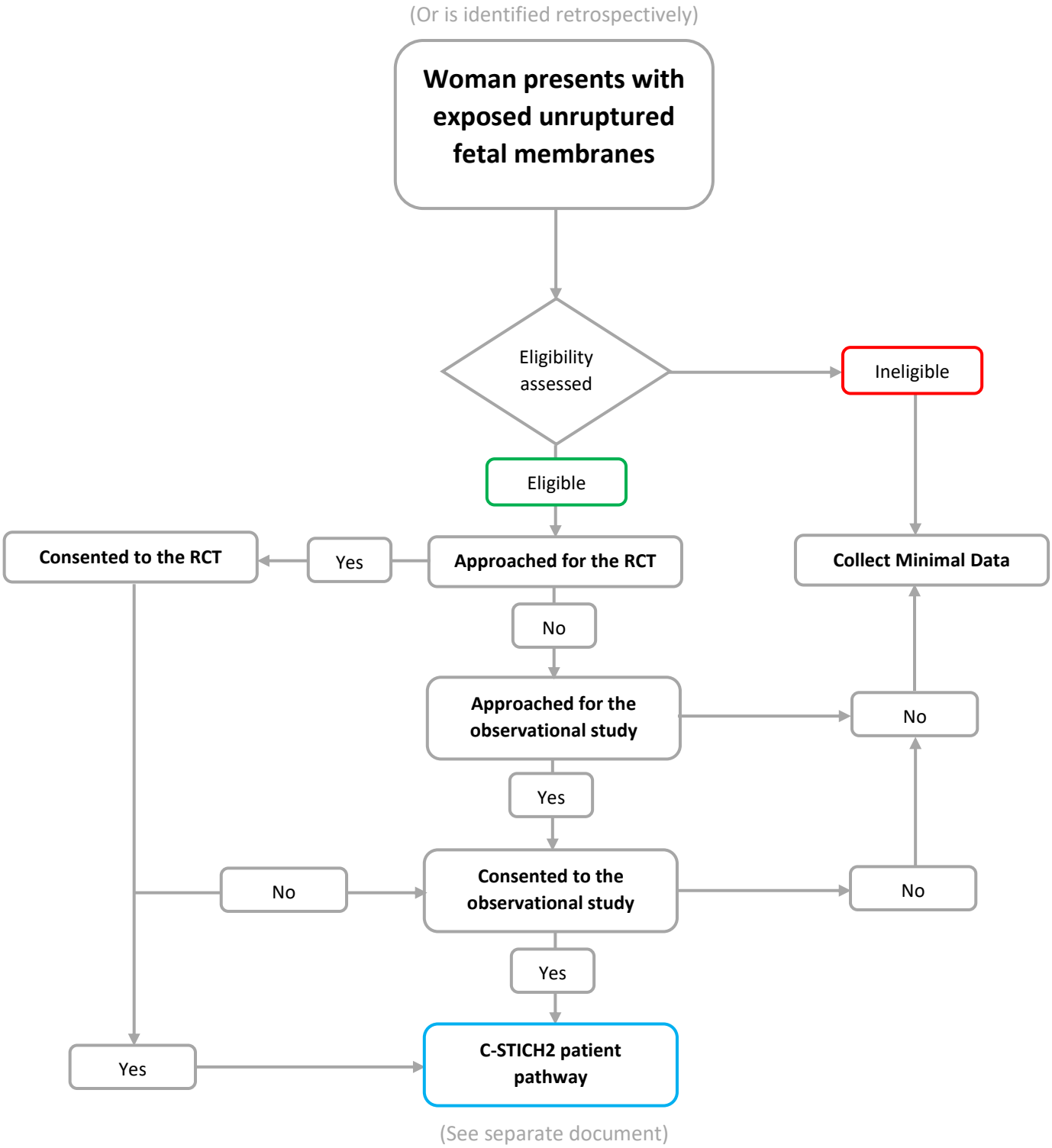
Lay Summary

A cervical cerclage is the placement of a stitch to keep the neck of the womb closed. A stitch can be placed in a planned way because of a risk of preterm birth based on a woman's pregnancy history or because the neck of the womb is shorter than normal on an ultrasound scan but still closed. Sometimes the neck of the womb can start to open and expose the bag of water around the baby. If this happens between 16 and 28 weeks of pregnancy, an emergency stitch is sometimes inserted to try to delay delivery. Prolonging the pregnancy so that the baby can be born when they are bigger and stronger may give them a better chance of surviving and suffering from fewer complications of prematurity. However, doctors do not know if an emergency cerclage works. There is some evidence it may prolong pregnancy but it is possible that it will also speed up delivery by causing infection or damage to the neck of the mother's womb. It is therefore very important to undertake a study to decide if emergency cerclages delay delivery, and if they do, whether this benefits the baby (and mother). The best way to work out if emergency cerclage works, and is safe, is to ask women to be randomly allocated to either emergency cerclage or no cerclage. This is what we need to do to ensure we know what is best for future women and babies to prevent harm. This study will ask women who have an open neck of the womb with the bag of waters around the baby coming through, to have either an emergency stitch or no emergency stitch. Which treatment they will receive will be decided by a process that randomly allocates a woman to one group or the other. All women in the study, irrespective of their allocated group, will be able to have other treatments that may help prolong pregnancy such as antibiotics, progesterone and medicines that stop the womb contracting. The study team will collect information about what happens to the mother and baby from their medical notes and talk to women about their experiences of taking part in the study. Where appropriate, families will be contacted at 2 years of age to assess how the babies are developing by a postal questionnaire completed by the carers.

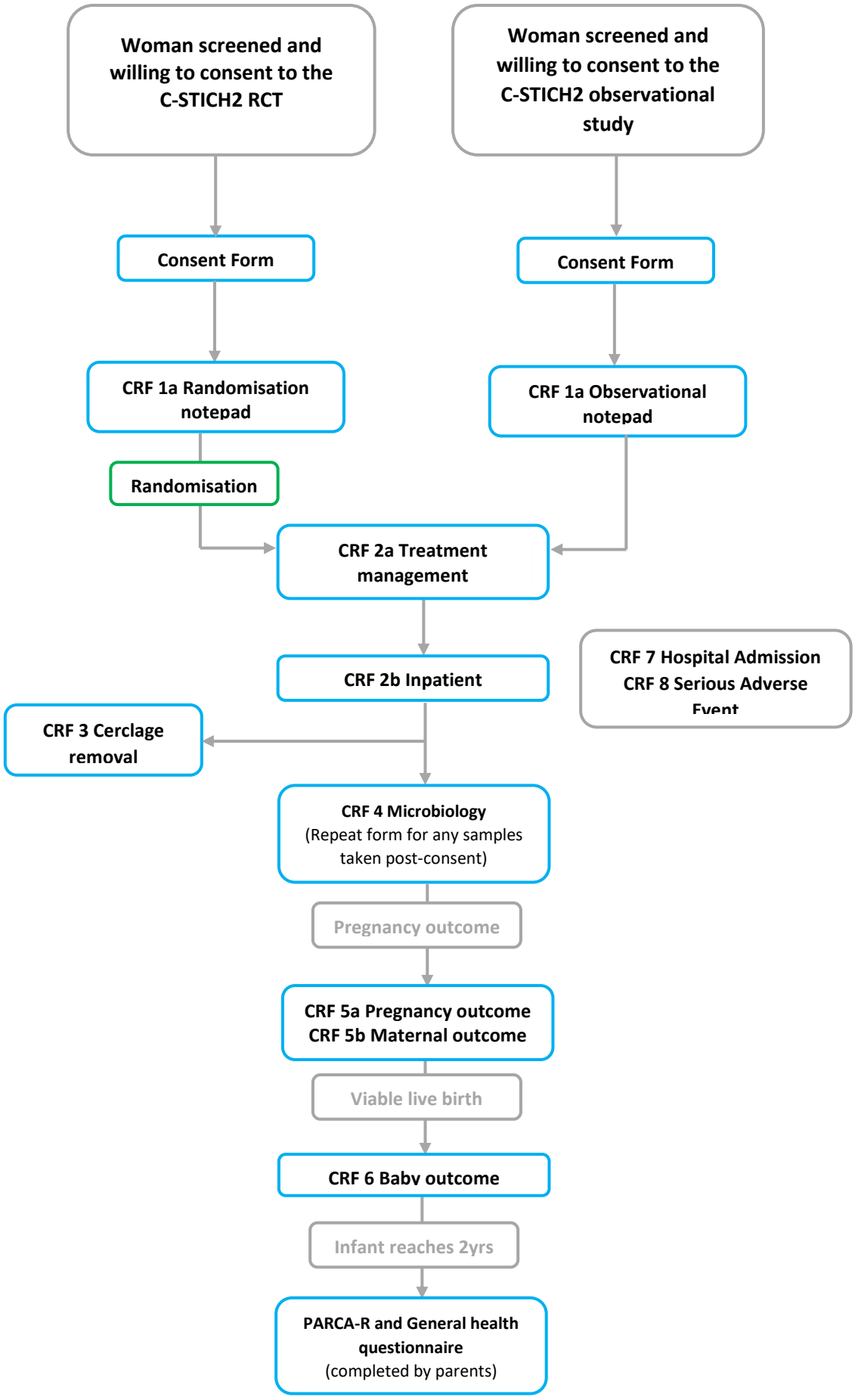
Trial Schema

<table>
<tr><td rowspan="2">Y1</td><td colspan="2">Study set up
Using the established network of over 60 maternity units from C-STICH.
We will aim to open 12 lead recruiting sites within the first 6 months</td></tr>
<tr><td></td><td></td></tr>
<tr><td rowspan="2">Y2</td><td>Recruitment
(pilot)</td><td>Qualitative study</td></tr>
<tr><td colspan="2">Pilot Assessment (TSC/DMC)</td></tr>
<tr><td rowspan="2">Y3</td><td rowspan="2">Recruitment
(to the full RCT)</td><td>Post-pilot implementation of changes</td></tr>
<tr><td>Recruitment
(to the observational study)</td></tr>
<tr><td rowspan="2">Y4</td><td rowspan="2"></td><td rowspan="2"></td></tr>
<tr><td></td></tr>
<tr><td rowspan="2">Y5</td><td colspan="2">Pregnancy follow-up</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td>Y6</td><td colspan="2">Two-year follow-up
PARCA-R and General health questionnaire</td></tr>
<tr><td>Y7</td><td colspan="2"></td></tr>
<tr><td></td><td colspan="2">Final Report</td></tr>
</table>

Screening Pathway



Main trial patient pathway



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1. BACKGROUND AND RATIONALE

1.1. Background

Second trimester miscarriage and very early pre-term birth (PTB) results in significant risks of morbidity and mortality to babies [2]. Cervical insufficiency is one important cause of PTB. An established treatment for cervical insufficiency is vaginal cervical cerclage (i.e. placement of a stitch around the cervix to keep it closed [3]). The majority of cervical cerclages are placed electively when cervical insufficiency has been suspected based on previous history or identification of a short but closed cervix in the current pregnancy.

In a situation where the cervix has opened and the fetal membranes are exposed, an emergency cervical cerclage (ECC) can be performed. This procedure aims to halt further cervical dilatation and prolong pregnancy, preventing miscarriage or PTB and thus potentially improving neonatal outcome. However, ECC has not been fully evaluated for clinical and cost effectiveness and carries risks to both the mother and baby [4]. These risks include cervical trauma, severe infection/sepsis and iatrogenic rupture of membranes during the procedure leading to fetal loss.

There remains uncertainty about both the immediate benefit and long-term development of babies born following an ECC. Specifically, in-utero infection may result in worsening neurological outcome [5, 6].

1.2. Trial Rationale

NICE guidance (2015) [7] on PTB prevention reviewed the evidence for ECC (one RCT of 23 women, and several retrospective cohorts [8]). They concluded that there was a possible positive effect, but that there was a need for further evidence and that "a RCT would best address this question, but a national registry of the most critical outcomes (neonatal mortality and morbidity, maternal morbidity) could also be considered". The evidence has also been summarised in a review by Namouz et al [4] who described the results of the only RCT conducted [8], comparing 1 group of 13 women (10 singleton and 3 twin pregnancies) who were allocated to emergency cerclage with 10 women (6 singleton and 4 twin pregnancies) who had bed rest only. All the participants received antibiotic treatment for 1 week, whereas the cerclage group also received indomethacin treatment.

The cerclage group did significantly better compared with the bedrest group in mean randomisation-to-delivery interval (54 vs 20 days, $p = 0.046$), preterm delivery before 34 weeks (54% vs 100%, $p = 0.02$), and a compound neonatal morbidity outcome that was defined as admission to the neonatal intensive care unit and/or

neonatal death (62.5% vs 100%; p = 0.02; relative risk, 1.6; 95% confidence interval, 1.1-2.3). However, no significant difference was found in neonatal survival (56.3% vs 28.6%). Concerns about this trial include the small sample size, fewer twin pregnancies in the cerclage group, and the use of indomethacin only in the cerclage group. The largest observational study was a retrospective cohort of 161 women comparing emergency cerclage versus bed rest and demonstrated an improved live birth rate (72% v 25% p<0.001) and prolongation of pregnancy in the cerclage group (41 days v 3 days p<0.001 [9]) both statistically significant findings. The event rate for our primary outcome (miscarriage, stillbirth, termination of pregnancy or neonatal death within 7 days of delivery) within this study was 28% in the cerclage group v 75% in bed rest group.

Smaller observational retrospective studies have found significantly increased interval from treatment-to-delivery and increased mean birth weight in the cerclage groups. In addition, higher neonatal survival rates and live birth rates in the cerclage group were observed. Like all observational studies, there is a potential for confounding by indication which makes this data difficult to interpret.

1.2.1. Justification for participant population

The participant population identified are those in whom an ECC may be considered appropriate. Eligibility criteria will be kept as broad as feasible to be generalisable to clinical practice.

1.2.2. Justification for design

Evidence for the effectiveness of ECC is limited due to the challenges that exist in undertaking a trial of its effectiveness, including: issues recruiting women to an RCT in this clinical situation, the relatively uncommon occurrence of the condition and the need for operator skill to perform ECC.

We recognise the challenges of this trial and therefore have detailed a clear pilot phase with a nested qualitative process evaluation. We have pre-specified continuation criteria that will establish whether an adequately sized RCT of ECC is feasible.

An RCT is the gold standard evidence required to determine effectiveness of an intervention and is therefore the optimal design of a study in this pilot phase. RCTs are a rigorous way of determining whether a cause-effect relationship exists between treatment and outcome. Non-randomized studies, can detect associations between an intervention and an outcome, but they cannot control for the possibility that the association was caused by a third (confounding) factor linked to both intervention and outcome.

If the pilot RCT demonstrates that continuation with the full RCT is not possible, consideration will be given to collecting data for a prospective cohort study, carefully controlling for potential confounders. If this does occur, a further detailed protocol will be developed.

1.2.3. Change to design following internal pilot

Recruitment figures, the minimal dataset, and qualiataive study were assessed as part of the pilot review. The trial management group, data monitoring committee, trial steering committee and and the trial funders have agreed to modify the study design to include a consented observation cohort study, collecting all outcomes.

This decision recognises that a RCT remains the gold standard of evidence required to inform management andwe remain committed to delivering a RCT. Yet, while their remains uncertainty with regard to the incidence of the condition and the natural course of the condition it is difficult to achieve overall sample size and anticipated power. Therefore in conjunction to the RCT a prospective non-randomised consented cohort study will be introduced, offferng participation to all eligible women who decline to join the trial, or women who were not approached regarding the trial before a management plan for the condition was initiated.

1.2.4. Choice of intervention

ECC aims to close the dilated cervix and replace the bulging fetal membranes. There are risks associated with the placement of an ECC and these will be discussed further in section 3.5 assessment of risk.

Other interventions have been investigated in this clinical situation such as progesterone, antibiotics and tocolytics. These are non-mechanical interventions and evidence for their effectiveness is limited. This trial will be pragmatic in nature allowing the use of these adjuncts in both arms prior to and following randomisation.

2. **AIMS AND OBJECTIVES**

2.1. **Aims and Objectives**

Aims:

The overarching aim of this project is to evaluate whether ECC can improve outcomes for mothers and babies' in women who present with cervical dilatation and exposed, unruptured fetal membranes.

The project includes an internal pilot, nested qualitative process evaluation and cost-effectiveness analysis.

Pilot objectives:

The pilot stage of this trial will provide important information for the continuation of the full trial including to:

a) Ascertain if the trial and trial processes are acceptable to women, including the ability to recruit and randomise women.

b) Assessment of whether the event rate of the primary outcome is compatible with the estimate used in the sample size calculation.

c) Establish if clinicians are in equipoise and are willing to randomise to a RCT.

Objectives of the full randomised controlled trial:

- To determine whether an ECC reduces pregnancy loss (miscarriage, termination of pregnancy, stillbirth or neonatal death within 7 days of delivery) in women who present with cervical dilatation and exposed, unruptured fetal membranes between 16+0 and 27+6 weeks.
- To follow up all surviving babies to 2 years of age to determine their general health and medium term neurodevelopmental outcomes.
- To determine the complication rates of ECC:
    A) Including the number of women with iatrogenic rupture of membranes during the procedure.
    B) The incidence of insertion failure.
    C) To explore predictors of successful ECC placement such as magnitude of dilatation.

Obectives for the observational cohort (following completion of the internal pilot):

The objectives of the cohort study are primarily the same as the RCT, its addition is to supplement the evidence collected in the RCT. Thefore there is overlap between the RCT and cohort objectives.

To determine whether an ECC reduces pregnancy loss (miscarriage, termination of pregnancy, stillbirth or neonatal death within 7 days of delivery) in women who present with cervical dilatation and exposed, unruptured fetal membranes between 16+0 and 27+6 weeks.

- To follow up all surviving babies to 2 years of age to determine their general health and medium term neurodevelopmental outcomes.
- To determine the complication rates of ECC:
    A) Including the number of women with iatrogenic rupture of membranes during the procedure.
    B) The incidence of insertion failure.

C) To explore predictors of successful ECC placement such as magnitude of dilatation.

- To allow full outcome and two year follow up from women who are not partaking in the C-STICH2 randomised controlled trial to ensure maximal information is ontained within this research project.

3. TRIAL DESIGN AND SETTING

3.1. Trial Design

A randomised, controlled multicentre trial with an internal pilot and nested qualitative process evaluation. Should benefit of ECC be demonstrated (either primary outcome or prolongation of gestation) a full cost effectiveness evaluation would also be performed.

Following review of the internal pilot, an observational cohort study was added to the study design to run in parallel to the RCT. This cohort study has been designed to allow longer term follow up of women and babies that have not been recruited to the RCT or had the opportunity to be recruited to the RCT.

3.2. Trial Setting

Maternity units within the UK, utilising but not limited to the network of 65 sites participating in C-STICH; a randomised controlled trial of suture type (monofilament vs braided) and its effect on preventing miscarriage and preterm birth in women undergoing an elective cervical cerclage (https://www.birmingham.ac.uk/research/activity/mds/trials/bctu/trials/womens/C-Stich/about.aspx).

It is anticipated that the majority of sites will run both the observational and RCT. Yet where a centre is unable to facilitate the RCT the observational study can run independently, this will ensure generalisability.

3.3. Identification of participants

Women who present to specialist preterm birth clinics, maternity triage assessment areas and delivery suites with preterm cervical dilatation and exposed, unruptured fetal membranes will be identified by the clinicians caring for them and the C-STICH2 teams will be informed. We will seek to identify lead clinicians at each centre that would routinely care for women with this condition to facilitate identification.

3.4. Additional studies

The project will include a number of additional studies:

- A qualitative process evaluation of the feasibility and acceptability of the trial (Section 21). This completed at the end of the internal pilot and information generated has informed ongoing study design. Details of the qualitative process evaluation remains in the protocol for completeness.

- A health economic evaluation (Section 22)

- An anonymised minimal data set for collection of outcomes for women who decline to participate or who are missed (Section 23)

3.5. **Assessment of Risk**

As ECC is already in use in current practice, the risk of participating in the trial is approximately the same as for women not participating within the trial.

The placement of an ECC is a challenging operation that attempts to replace the bulging fetal membranes and place the cerclage as close to the internal os as possible to close the cervix. There are thus associated risks including failure to replace the membranes and failure to place a cerclage, with increasing risk as cervical dilatation increases. Iatrogenic rupture of the fetal membranes during the procedure can occur causing miscarriage, or in ongoing pregnancies, a significant risk of infection and fetal pulmonary hypoplasia. Uncommon risks of the cerclage procedure for the mother include cervical laceration and general risks of surgery (i.e. anaesthetic risks, venous thromboembolism and anaphylaxis). The ECC will need to be removed prior to vaginal delivery and associated risks of removal include bleeding, cervical laceration, and retained suture thread. Difficult to remove sutures may require regional anaesthesia.

The causative process of cervical dilatation in this situation is unknown, with potential mechanisms being a weakness of the cervical structure (either acquired or congenital) and infection (commonly ascending from the vagina and/or urinary tract). With exposure of the fetal membranes to the vaginal mucosa, there is an additional increased risk of intra amniotic infection and maternal infection/sepsis. Thus, it may be that the placement of an ECC increases these risks further, and thus exposes the mother and fetus to the risk of infection and associated morbidity and mortality and potentially worsening outcomes.

These are accepted risks of the procedure of ECC and have all been previously described within the medical literature [10, 11]. Due to the uncommon nature of ECC and the heterogeneity within the population undergoing the procedure (e.g. previous cervical surgery, cervical dilatation, extent of membrane exposure to the vagina) the incidence of these has not been accurately ascertained. Informed consent for ECC procedure will be taken by the managing clinician as per standard care, following randomisation to an ECC, and thus the risks quoted to the women will be based on the literature and local data.

4. ELIGIBILITY

4.1. Eligibility criteria

4.1.1. Inclusion Criteria

- Women 16 years of age or older
- Cervical dilatation sufficient to allow exposure of the unruptured, fetal membranes at or below the level of the external os based on clinical judgement
- Singleton pregnancies
- Gestational age 16+0 to 27+6 weeks based on best estimate
- Able to give informed written consent.

4.1.2. Exclusion Criteria

- Contraindication to emergency cerclage as judged by the clinician
- Cervical cerclage (vaginal or abdominal) inserted earlier in this pregnancy or in a previous pregnancy and remains in situ.
- Gestational age < 16+0 weeks
- Gestational age ≥ 28+0 weeks
- Unable to give informed consent

4.2. Eligibility criteria for the observational cohort study

Women who fulfil the eligibility for the RCT but are not recruited, are eligible for the observational cohort study. Women are also eligible for the observational cohort if they have the primary condition and have received a intervention (including ECC) during the current hospital episode.

4.3. Co-enrolment

Women can take part in any observational study before or in conjunction with C-STICH2. Trials of preterm birth interventions and investigational medicinal products will be discussed on a case-by-case basis, by referral to BCTU and discussed with the CI.

5. CONSENT

5.1. Consent for the RCT

It will be the responsibility of the investigator to obtain written informed consent for each participant prior to performing any trial related procedure. The most senior clinician available should discuss the trial, conditional on them having received training by the C-STICH2 TMG or the lead clinician at each site. It is appreciated that the trial will be introduced at a difficult time for women and families and therefore it is desirable that the designated clinicians are experienced in counselling women at high risk of preterm delivery. A Participant Information Sheet (PIS) will be provided to facilitate this process.

Clinician's will ensure that they adequately explain the aim of the trial, the trial treatment, anticipated benefits and the potential risks of taking part in the trial to the women. The PIS details the risks and benefits of ECC and the clinician will discuss these prior to consent for the trial.

Clinician's will also explain that participation is voluntary and that the woman is free to decline to take part and may withdraw from the trial at any time.

The woman will be given appropriate time to read the PIS and to discuss participation with others outside of the site research team, given the time constraints of the situation.

The woman will be given the opportunity to ask questions before signing and dating the latest version of the Consent Form. If the woman agrees to participate, they will be asked to initial each box of the Informed Consent Form (ICF), sign and date, and the clinician will then sign and date. A copy of the ICF will be given to the participant, a copy will be filed in the medical notes, a copy sent to BCTU and the original placed in the Investigator Site File (ISF). Once the participant is randomised into the trial, the participant's trial number will be entered on the ICF.

Details of the consent discussions will be recorded in the woman's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to participant and version number of ICF signed and date consent received. Where consent is obtained on the same day that the trial related assessments are due to start, a note should be made in the medical notes as to what time the consent was obtained and what time the procedures started. To facilitate this process, sites will be provided with consent stickers for the medical records.

Throughout the trial, the woman will have the opportunity to ask questions about the trial. Any new information that may be relevant to the woman's continued participation will be provided.

Electronic copies of the PIS and ICF will be available from the Trials Office. Details of all patients approached about the trial will be recorded in the minimal dataset. The women's General Practitioner (GP) will also be informed that they are taking part.

5.2. **Consent fot the observational study**

It will be the responsibility of the investigator to obtain written informed consent for each participant prior to enrolling . Research staff and clinicians who are designated by the P.I to discuss the cohort study should approach women and explain the study. It is appreciated that the study will be introduced at a difficult time for women and families and therefore it is desirable that the designated personel are experienced in counselling women at high risk of preterm delivery. A PIS will be provided to facilitate this process.

Personal will also explain that participation is voluntary and that the woman is free to decline to take part and may withdraw from the study at any time.

The woman will be given appropriate time to read the PIS and to discuss participation with others outside of the site research team. The consent discussion can take place after the initial management of the condition has commenced whether that be a ECC or expectant management.

The woman will be given the opportunity to ask questions before signing and dating the latest version of the Consent Form. If the woman agrees to participate, they will be asked to initial each box of the Informed Consent Form (ICF), sign and date, and the researcher will then sign and date. A copy of the ICF will be given to the participant, a copy will be filed in the medical notes, a copy sent to BCTU and the original placed in the Investigator Site File (ISF). Once the participant is recruited into the trial, the participant's trial number will be entered on the ICF.

Details of the consent discussions will be recorded in the woman's medical notes. This will include date of discussion, the name of the study, summary of discussion, version number of the PIS given to participant and version number of ICF signed and date consent received. To facilitate this process, sites will be provided with consent stickers for the medical records.

Throughout the study, the woman will have the opportunity to ask questions about the study. Any new information that may be relevant to the woman's continued participation will be provided.

Electronic copies of the PIS and ICF will be available from the Trials Office. Details of all patients approached about the trial will be recorded in the minimal dataset. The women's General Practitioner (GP) will also be informed that they are taking part.

6. **RECRUITMENT, ENROLMENT AND RANDOMISATION**

6.1. **Recruitment into the RCT**

Potentially eligible women will be identified by maternity triage and labour ward teams (doctors, midwives, researchers) and notified to the research team and local lead clinician.

They will be clearly advised that participation in the study is entirely voluntary with the option of withdrawing from the study at any stage, and that participation or non-participation will not affect their usual care. All women will be provided with the PIS and given time to consider their involvement.

If happy to participate in the study, women will be consented to the study and randomised to allow the management plan to be communicated to the women and clinicians as soon as possible.

6.2. **Recruitment into the observational cohort study**

Potentially eligible women will be identified by maternity triage, labour ward teams (doctors, midwives, researchers), theatre teams and antenatal ward rounds and local research teams will be notified.

They will be clearly advised that participation in the study is entirely voluntary with the option of withdrawing from the study at any stage, and that participation or non-participation will not affect their usual care. All women will be provided with the PIS and given time to consider their involvement.

If happy to participate in the study, women will be consented to the observational study.

6.3. **Enrolment and Screening**

If the clinician deems an emergency cervical cerclage to be an appropriate management option, then the woman will be potentially eligible for the trial.

Information regarding women with the presenting condition of "*Cervical dilatation sufficient to allow exposure of the unruptured, fetal membranes at or below the level of the external os based on clinical judgement"* will be entered onto an online screening database at the Birmingham Clinical Trials Unit (BCTU). Women will be entered the following categories:

- Have presenting condition, fulfil eligibility criteria and consent to randomisation
- Have presenting condition, fulfil eligibility criteria but do not consent to randomisation, but consent to observational cohort.
- Have presenting condition, fulfil eligibility criteria but do not consent to randomisation or the observational cohort.

- Have presenting condition, fulfilled the eligibility criteria during this hospital episode, butwere not approached to enter the RCT and have consented to the observational cohort. .
- Have presenting condition but do not fulfil eligibility criteria for the trial or the observational cohort.

Each entry onto the screening database will be issued a screening number (SNO). This SNO will be entered onto the sites screening and enrolment log which will be held and be accessible at site only as it contains patient identifiers. Patient identifiable data will never be shared or transferred to BCTU for women who have not consented to the RCT or observational study.

Consent will not be required for entry onto the screening database and only anonymised data will be collected, which includes date of presentation, site, gestation, and if relevant, reason for ineligibility or non-participation. All women screened will have their pregnancy demographics, treatment and pregnancy outcomes collected and uploaded to the BCTU database without any identifiers, to allow important information regarding the prevalence, natural history and outcomes from the condition to be collected.

Following entry of the screening details on the BCTU database there will be a seamless transition to the randomisation system for women who consent to enter the trial or the observational study (if consented).

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6.4. **Randomisation**

Randomisation will be provided by a secure online randomisation system at the BCTU. Unique login usernames and passwords will be provided to those who wish to use the online system and who have been delegated the role of randomising participants into the study, as detailed on the C-STICH2 Trial Signature and Delegation Log. The online randomisation system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance. The randomisation website is (www.trials.bham.ac.uk/cstich2) A free telephone randomisation service (0800 953 0274) is available Monday to Friday, 09:00 to 17:00 UK time, except for bank holidays and University of Birmingham closed days.

After eligibility has been confirmed and informed consent has been received, the women can be randomised into the trial. Randomisation Notepads will be provided to investigators and may be used to collate the necessary information needed prior to randomisation. All questions and data items on the Randomisation Notepad will need to be answered before a Trial Number (TNO) and allocation can be given. If data items are missing, randomisation will be suspended, but can be resumed once the information is available. Only when all eligibility criteria and baseline data items have been provided will a Trial Number be allocated.

Participants will be randomised at the level of the individual in a 1:1 ratio to either ECC or expectant management (monitoring). A minimisation algorithm will be used within the online randomisation system to ensure balance in the treatment allocation with regard to relevant pre-specified variables:

- Site
- Gestational age (16+0 - 19+6 weeks; 20+0 - 23+6 weeks; 24 +0 - 27+6 weeks)
- Cervical dilatation at randomisation (≤3cm, ≥4cm , fully dilated - minimal cervix felt)

A 'random element' will be included in the minimisation algorithm, so that each patient has a probability (unspecified here), of being randomised to the opposite treatment that they would have otherwise received. Full details of the randomisation specification will be stored in a confidential document at BCTU.

Following randomisation, a confirmatory e-mail will be sent to the randomising clinician, local PI, local research nurse/ research midwife, trial inbox and CI.

6.5. **Entry into the observational study**

After eligibility has been confirmed and informed consent has been received, the women can be entered into the study. Observational Notepad will be provided to investigators and should be used to collate the necessary information needed to confirm entry into the observationl cohort study. All questions and data items on the Observational Notepad will need to be answered before a Trial Number (TNO) can be given.

6.6. **Informing the participant's GP**

If the woman has agreed, her GP will be notified that they are in C-STICH2 study using the **GP Letter** sent by the site**.**

6.7. **Blinding**

Clinicians and women cannot be blinded to the intervention they have received. The evaluation is between a surgical procedure and expectant management.

Pregnancy outcome data will be collected from the medical records by an independent research midwife/nurse or assistant, during the collection of this data it will likely become apparent which group the women was randomised too. It is appreciated that this potentially can introduce a source of bias; however, many of

the outcomes being collected, including the primary outcome, are not susceptible to observer bias.

7. **TRIAL TREATMENT / INTERVENTION**

Women randomised to the ECC group will receive the treatment as soon as practical and feasible at the trial site. Informed consent for the ECC procedure will be taken by the managing clinician as per standard care, following randomisation to an ECC, and thus the risks quoted to the women will be based on the literature and local data. The intervention should be performed by a clinician experienced in the placement of ECCs who will need to be nominated on the delegation log for this task. If a woman allocated to ECC does not receive the intervention within 72 hours of randomisation, this will be recorded as a protocol deviation. After 72 hours the ECC should still be inserted at the earliest opportunity, unless the clinician in charge of the woman's care believes that the clinical situation has significantly changed such that an ECC is no longer appropriate.

Preoperative management is at the discretion of the clinician caring for the woman according to standard clinical practice.

Intraoperative management is at the discretion of the clinician including the surgical technique used for both replacement of the membranes and insertion of the suture, choice of suture thread, use of antibiotics and indomethacin.

Post-operative management is at the discretion of the clinician including the continued use of antibiotics, indomethacin and the use of progesterone and bed rest via hospital admission.

Details of pre, intra, and post-operative management will be collected via the CRFs.

Women allocated to expectant management who receive an ECC during the pregnancy will be considered a protocol deviation.

8. OUTCOME MEASURES AND STUDY PROCEDURES

The outcomes detailed below will be the same for the RCT and the observational cohort.

8.1. Primary Outcome

- Pregnancy loss (miscarriage, termination of pregnancy and perinatal mortality, including any stillbirth or neonatal death within 7 days of delivery).

8.2. Secondary Outcomes

Maternal

- Pregnancy loss (miscarriage, termination of pregnancy and perinatal mortality, including any stillbirth or neonatal death in the first week of life). Excluding those due to congenital anomalies (chromosomal and/or structural) assessed via death certification.
- Time from conception to pregnancy end (any reason)
- Miscarriage & pre-viable neonatal death (defined as delivery <24 weeks)
- Stillbirth (defined as intrauterine death ≥24 weeks)
- Gestation at delivery
- Pre-term delivery (pre-specified groups of ≤28/≤32/≤37 weeks))
- Maternal sepsis (at any time in pregnancy and until discharge from hospital postnatally)
- Preterm (<37 weeks) pre labour rupture of membranes (>24 hours prior to delivery) (PPROM) adjusting for gestational age at occurrence of membrane rupture
- Mode of initiation of birth (spontaneous or iatrogenic)
- Indication for iatrogenic delivery (maternal and/or fetal)
- Mode of delivery (vaginal or operative vaginal or caesarean)
- Cerclage placement complications assessed as a composite and individually:
    - cervical laceration
    - bleeding from cervix
    - ruptured membranes
    - bladder injury
- Cerclage removal complications assessed as a composite and individually:
    - cervical tears

    - difficulty in removal defined as requiring unexpected anaesthesia or unexpected dissection of suture
- Suspected or confirmed chorioamnionitis (during pregnancy and up to 7 days postnatally)
- Maternal admission to HDU or ITU pre-delivery
- Maternal admission to HDU or ITU post-delivery
- Serious adverse events (see section 10)

Neonatal

- Early neonatal death (defined as a death within 7 days after delivery)
- Late neonatal death (defined as a death beyond 7 days and before 28 days after delivery) (NHS data check)
- Early neonatal death (defined as a death within 7 days after delivery excluding those secondary to congenital anomalies)
- Late neonatal death (defined as a death beyond 7 days and before 28 days after delivery excluding those secondary to congenital anomalies)
- Birth weight adjusted for gestational age and sex (in live births ≥24 weeks)
- Small for gestational age (<10th centile; in live births ≥ 24 weeks)
- Advanced resuscitation at birth (assisted ventilation and/or drug administration and/or cardiac compressions)
- Admission to specialist care (SCBU/NICU/HDU/transitional care) collected from birth until discharge from hospital or 28 days post EDD (whichever comes sooner).
- Length of stay in each additional specialist care setting
- Suspected sepsis (clinically diagnosed defined as commenced on intravenous antibiotics for >48 hours after birth) collected from birth until discharge from hospital or 28 days post EDD (whichever comes sooner).
- Confirmed sepsis (positive microbiology) collected from birth until discharge from hospital or 28 days post EDD (whichever comes sooner).
- Brain injury (defined as any intraventricular haemorrhage (IVH) (excludes subependymal haemorrhages), parenchymal cystic or haemorrhagic lesion or persistent ventriculomegaly (VI >97th percentile)) collected from birth until discharge from hospital or 28 days post EDD (whichever comes sooner).
- Respiratory support (ventilation/CPAP) from birth until discharge from hospital or 28 days post EDD (whichever comes sooner).
- Days on respiratory support
- Supplementary oxygen requirements at 36 weeks corrected gestational age

- Necrotising enterocolitis (Bell's stage 2 or 3) collected from birth until discharge from hospital or 28 days post EDD (whichever comes sooner).
- Retinopathy of prematurity requiring laser treatment collected from birth until discharge from hospital or 28 days post EDD (whichever comes sooner).
- Disabilities collected from birth until discharge from hospital or 28 days post EDD (whichever comes sooner).
- Congenital abnormalities collected from birth until discharge from hospital or 28 days post EDD (whichever comes sooner).
- Serious adverse events (see Section 10)

Paediatric Outcomes

- Death at greater than 28 days until 2 years (NHS data check)
- Two-year outcomes collected through a parent completed general health questionnaire and PARCA-R.

8.3. Minimal dataset outcomes

Maternal

- Pregnancy loss (miscarriage, termination of pregnancy and perinatal mortality, including any stillbirth or neonatal death within 7 days of delivery).
- Time from conception to pregnancy end (any reason).
- Miscarriage & pre-viable neonatal death (defined as delivery <24 weeks).
- Stillbirth (defined as intrauterine death ≥24 weeks).
- Gestation at delivery (Live births ≥24 weeks).
- Pre-term delivery (pre-specified groups of ≤28/≤32/≤37 weeks).
- Preterm (<37 weeks) pre labour rupture of membranes (≥2 days prior to delivery) (PPROM).
- Gestation at PPROM (≤28/≤32 weeks).
- Mode of initiation of birth (spontaneous or iatrogenic).
- Mode of delivery (vaginal or operative vaginal or caesarean).

Neonatal

- Birth weight adjusted for gestational age and sex (in live births ≥24 weeks).
- Small for gestational age (<10th centile; in live births ≥24 weeks).

9. **SCHEDULE OF ASSESSMENTS**

Table 1: RCT

Visit	*Screening Consent Randomisation*	*Day 1-3*	*Cerclage removal if required*	*Birth*	*Maternal discharge from hospital after delivery*	*Neonatal discharge from hospital*	*28 day neonatal*	*Two year paediatric follow-up*
Screening check	X							
Eligibility check	X							
Valid informed consent	X							
CRF 1a: Randomisation	X							
CRF 2a: Treatment management		X						
CRF 2b: in-patient management		X						
CRF 3: Cerclage removal in cerclage arm			X					
CRF 4: Microbiology	X	X	X	X	X	X	X	
CRF5a: Delivery details				X				
CRF5b: Maternal outcome					X			
CRF6: Baby outcome						X	X	
Paediatric long term follow-up								X

Table 2: Observational cohort study

Visit	*Screening Consent*	*Day 1-3*	*Cerclage removal if required*	*Birth*	*Maternal discharge from hospital after delivery*	*Neonatal discharge from hospital*	*28 day neonatal*	*Two year paediatric follow-up*
Screening check	X							
Eligibility check	X							
Valid informed consent	X							
CRF 1a:Observational Notepad	X							
CRF 2a: Treatment management		X						
CRF 2b: in-patient management		X						
CRF 3: Cerclage removal (if applicable)			X					
CRF 4: Microbiology	X	X	X	X	X	X	X	
CRF5a: Delivery details				X				
CRF5b: Maternal outcome					X			
CRF6: Baby outcome						X	X	
Paediatric long term follow-up								X

9.1. **Participant Withdrawal**

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation.

Participants should be aware at the beginning that they can freely withdraw (discontinue participation) from the trial or observational cohort (or part of) at any time without consequence to their care.

Types of withdrawal as defined are:

- The participant would like to withdraw from trial treatment (RCT only), but is willing to be followed up in accordance with the schedule of assessments and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected and used in the trial analysis)

- The participant would like to withdraw from trial treatment (RCT only) and is not willing to be followed up in any way for the purposes of the trial/study and for no further data to be collected (i.e. only data collected prior to the withdrawal can be used in the trial analysis)

- The participant has had the trial treatment (RCT only) but would like to withdraw from part or all of the follow-up

Or

- The participant wishes to withdraw completely (i.e. from trial treatment (RCT only) and all follow up) and is not willing to have any of their data, including that already collected, to be used in any future trial analysis

The details of withdrawal (date, reason and type of withdrawal) should be clearly documented in the source data.

10. ADVERSE EVENT REPORTING FOR THE RCT

10.1. Reporting Requirements

The collection and reporting of Adverse Events (AEs) will be in accordance with the UK Policy Framework for Health and Social Care (2017) and the requirements of the Health Research Authority (HRA). Definitions of adverse events are given in the Table 3.

Table 3: General definitions for adverse events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a trial participant, which is identified at any point between randomisation and 6 weeks postpartum, and does not necessarily have a causal relationship with the intervention.
Serious Adverse Event (SAE)	Any AE that: • results in death; • is life-threatening*; • requires hospitalisation or prolongation of existing hospitalisation (with exceptions†); • results in persistent or significant disability or incapacity; or • is considered medically significant by the investigator
Related Event (AE or SAE)	An event (AE or SAE) which resulted from the administration of any of the research procedures.
Protocol-exempt SAE	A SAE that is listed in the protocol as not requiring reporting on a separate SAE form.†
Expeditable SAE	A SAE that requires reporting on a SAE form.
Unexpected SAE	A SAE that is not listed in the protocol as an expected occurrence.‡
Unexpected and Related SAE	A SAE that meets the definition of both an Unexpected SAE and a Related SAE
** Life-threatening in the definition of a SAE refers to an event in which the mother was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.* *† Some SAEs are 'protocol-exempt' SAEs because they are either expected given the high-risk nature of C-STICH2 participants, or unrelated to the C-STICH2 intervention (See Section 10.3.2).* *‡ See Section 10.3.2.*	

10.2. **Adverse Events (AE) Requiring Reporting in C-STICH2**

There are certain AEs which are commonly experienced in participants who are pregnant, in the postpartum period, and in premature neonates. As these events are well characterised, it is unlikely that this trial will reveal any new safety information relating to this intervention. The reporting of AEs will therefore not affect the safety of participants or the aims of the trial and these will be collected through the CRFS. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the trial participant and this should be documented in the source data with reference to the protocol.

Given the high incidence of AEs anticipated in the high-risk population of women and neonates, only specific Serious AEs are reportable to the C-STICH2 Trial Office on the SAE Form (See Section 10.3).

10.3. **Serious Adverse Advents (SAE)**

All events that meet the definition of serious will be collected and recorded in the participant notes.

10.3.1. SAEs Requiring Expedited Reporting in C-STICH2 on the SAE form.

All maternal deaths will be reported to BCTU on the SAE Form irrespective of whether the death is related to pregnancy, the cerclage procedure, or an unrelated event. If a participant dies, any post-mortem findings must be provided to BCTU. BCTU will report all deaths to the DMEC, chief investigator and sponsor for continuous safety review.

Expected SAEs that are serious and still **requiring expedited reporting** include, but are not limited to, the following:

- Maternal admission requiring care within an HDU/ITU setting
- Other conditions threatening the life of the mother
- Complications from anaesthesia, anaphylaxis or general surgical complications from the cerclage insertion (e.g. venothromoboembolism post-cerclage insertion)

10.3.2. SAEs requiring reporting in C-STICH2 on the CRF.

Specific serious adverse events are outcomes of the trial and, although serious in nature, will be collected through the case report forms. A list of these expected serious adverse events are given below and require documentation in the source data, but do **not** need additionally expedited reporting on a SAE form, these include:

- Miscarriage
- Stillbirth

- Neonatal death prior to discharge from hospital after birth
- Prolonged hospital admission for observation for threated miscarriage or preterm birth
- Admission to hospital for delivery of the baby
- Iatrogenic rupture of membranes during the placement of the ECC
- Severe cervical lacerations at time of procedure or following labour with a cervical suture in situ
- Bladder injury as a result of the cerclage procedure
- Premature rupture of membranes following ECC procedure
- Admission to hospital for suture removal
- Anaesthetic for suture removal
- Caesarean section
- Congenital malformations, abnormalities identified on the mid trimester scan will not be recorded as SAEs. Only congenital abnormalities first identified in the neonatal period should be considered SAEs.
- Extended hospital stay of the mother due to the need to keep her baby in hospital
- Antepartum haemorrhage (APH) not requiring early delivery
- Postpartum haemorrhage (PPH) where a massive obstetric haemorrhage status is not declared
- Treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the pregnancy
- Neonatal admission to the neonatal care unit

All serious adverse events other than those listed above are considered to be expeditable and require reporting on the SAE Form to the C-STICH2 trial office.

10.4. **Reporting period**

Maternal SAEs should be collected from randomisation into the trial until discharge from hospital. Neonatal SAEs should be collected from birth until discharged from hospital, 28 days post delivery or the estimated date of delivery, whichever is sooner.

10.5. **Reporting Procedure - At Site**

10.5.1. Serious Adverse Events

On becoming aware that a participant has experienced an expeditable SAE (Section 10.3), the local PI or delegate(s) should report the expeditable SAE to: (i) their own Trust in accordance with local practice, and (ii) the C-STICH2 trial office at the

BCTU. This must be done within **24 hours** of the Investigator or delegate becoming aware of the event.

To report an expeditable SAE to the C-STICH2 office, the Investigator or delegate(s) must complete, date and sign the C-STICH2 SAE form. The completed form, together with any other relevant data, should be sent to the C-STICH2 trial team within **24 hours** of first becoming aware of the event.

To report an SAE, send a copy of the C-STICH2 SAE Form to:

c-stich2@trials.bham.ac.uk

On receipt of an SAE form, the BCTU trials team will allocate each SAE a unique reference number and return this via email to the site as proof of receipt. If the site has not received confirmation of receipt of the SAE from the BCTU or if the SAE has not been assigned a unique SAE identification number, the site should contact the BCTU trials team within one working day. The site and the BCTU trials team should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the Site File.

Where an SAE Form has been completed by someone other than the Principal Investigator, the original SAE form will be required to be countersigned by the Investigator to confirm agreement with the causality and severity assessments.

10.5.2. Assessment of Causality (Relatedness) by the PI

When completing the SAE form, the PI will be asked to define the nature of the seriousness and causality (relatedness; see Table 2) of the event. In defining the causality, the PI must consider if any concomitant events or medications may have contributed to the event and, where this is so, these events or medications should be reported on the SAE form. It is not necessary to report concomitant events or medications which did not contribute to the event. As per Table 4 below, all events considered at the site to be 'possibly', 'probably', or 'definitely' related to the intervention will be reported by the C-STICH2 trial office as 'related'; all events considered at site to be 'unlikely' or 'unrelated' to the intervention will be reported by the C-STICH2 trials office as 'unrelated'. The same categorisation should be used when describing all AEs in the source data

Table 4: Categorisation of causality (relatedness) for AEs and SAEs

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out	**Related**
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely	
Possibly	There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after the intervention was started). However, the influence of other factors may have contributed to the event (e.g., the patient's clinical condition, other concomitant events)	
Unlikely	There is little evidence to suggest there is a causal relationship (e.g., the event did not occur within a reasonable time after the intervention was started). There is another reasonable explanation for the event (e.g., the patient's clinical condition, other concomitant treatments)	**Unrelated**
Unrelated	There is no evidence of any causal relationship	

10.5.3. Provision of follow-up information

Following reporting of an SAE for a participant, the participants should be followed up until resolution or stabilisation of the event. Follow-up information should ideally be provided on a new SAE Form, using the SAE reference number provided by the BCTU trials team. Once the SAE has been resolved, all follow-up information has been received and the paperwork is complete, the original SAE form that was completed at site must be returned to the BCTU trials office and a copy kept in the Site File.

10.6. **Reporting Procedure - BCTU Trials Team**

On receipt of an SAE form from the site, the BCTU trials team will allocate each SAE form with a unique reference number and enter this onto the SAE form in the section for office use only. The SAE form (containing the unique reference number completed) will be forwarded to the site as proof of receipt within one working day. The SAE reference number will be quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the TMF.

On receipt of an SAE Form, the Chief Investigator (CI) or delegate(s) will independently determine the causality of the SAE, using the same criteria as outlined in Table 2, Section 10.5.2. The causality assessment given by the PI will not be downgraded by the CI or delegate(s). If the CI or delegate(s) disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

10.6.1. Assessment of Expectedness by CI

The CI or delegate(s) will also assess all related SAEs for expectedness with reference to the criteria provided in Table 5. The CI may request further information from the clinical team at site. This information should be made available immediately upon request. If the SAE is confirmed to be unexpected (i.e., is not defined in the protocol as an expected event, as in Section 10.3), it will be classified as an Unexpected and Related SAE.

Table 5: Definition of expectedness for SAEs

Category	Definition
Expected	A SAE that is classed in nature as serious and is consistent with the list of expected SAEs defined in the protocol.
Unexpected	A SAE that is classed in nature as serious and which is inconsistent with the list of expected SAEs defined in the protocol.

10.6.2. Reporting SAEs to third parties

If an Unexpected and Related SAE occurs, BCTU will report them to the PI, main REC, and Sponsor within 15 days; a copy of any such correspondence will be filed in the ISF and TMF. In addition, if an additional, significant safety issue is identified during the course of the trial, BCTU will notify the PI, main REC, and Sponsor immediately; a copy of any such correspondence will be filed in the ISF and TMF.

The independent DMC for the C-STICH2 trial will review SAEs at their meetings.

10.7. **Urgent Safety Measures**

If any urgent safety measures need to be taken by the BCTU, the Unit shall act immediately, and in any event no later than three days from the date the measures are taken, give written notice to the REC of the measures taken and the circumstances giving rise to those measures.

11. ADVERSE EVENT REPORTING FOR OBSERVATIONAL COHORT

No adverse events will be collected for the observational cohort.

12. DATA HANDLING AND RECORD KEEPING

12.1. Source Data

In order to allow for the accurate reconstruction of the trial and clinical management of the woman, source data will be accessible and maintained. The source for all data other than the maternal questionnaire will be the woman's medical notes and the neonatal notes. The maternal questionnaire is source data, being a participant reported outcome, which will be stored at site or at the University of Birmingham.

12.2. Case Report Form (CRF) Completion

Data reported on each form will be consistent with the source data and any discrepancies will need to be clarified by site staff. All missing and ambiguous data will be queried by the BCTU staff with site staff via a data clarification form (DCF). Staff delegated to complete CRFs will be trained initially via a site initiation meeting or by other trained members at each site to adhere to procedures for:

- CRF completion and corrections;
- Date format and partial dates;
- Time format and unknown times;
- Rounding conventions;
- Trial-specific interpretation of data fields;
- Entry requirements for concomitant medications (generic or brand names);
- Which forms to complete and when;
- What to do in certain scenarios, for example when a woman withdraws from the trial;
- Missing/incomplete data;
- Completing SAE forms and reporting SAEs; and
- Protocol and Good Clinical Practice (GCP) non-compliances.

In all cases, it remains the responsibility of the site's PI to ensure that the CRF has been completed correctly and that the data are accurate. This will be evidenced by the signature of the site's PI, or delegate(s), on the CRF.

12.3. Participant completed Questionnaires

When the surviving children reach two years of age, their main caregiver will be sent a general health questionnaire and a PARCA-R questionnaire directly from BCTU. The questionnaires should be completed by the main caregiver and returned to BCTU and each form will include options for return and a self-addressed envelope for postage.

Telephone contact will be made by the research team at neonatal discharge confirming consent and follow up arrangements. Further contact at six, twelve and eighteen months of age, will be made by a combination of sending cards and telephone contact. For each completed questionnaire a toy/shopping voucher will be sent to the main caregiver.

Any data which is unobtainable from either the continuing care site or the recruiting site will be sought from the NHS Digital (England and Wales) or ISD Scotland). NHS numbers assigned to the participant's babies will be passed on to NHS Digital or ISD Scotland with a view to obtaining any corresponding death information. The participant will be made aware of our intentions to request data from the continuing care site and / or NHS Digital or ISD Scotland in the Participant Information Sheet and their agreement will be recorded on the consent form.

12.4. **Data Management**

Processes will be employed to facilitate the accuracy of the data included in the final report. These processes will be detailed in the trial specific data management plan including a critical data item SOP. Coding and validation will be agreed between the trial coordinator, statistician and programmer, and the trial database will be signed off once the implementation of these has been assured.

Electronic Case Report Forms will be entered online at https://www.trials.bham.ac.uk/cstich2.

Authorised staff at sites (and at the trials office) will require an individual secure login username and password to access this online data entry system. Those entering data will receive written work instructions on the process (a copy of which should be filed in the ISF and TMF). CRFs should be filed within the ISF.

If changes need to be made to a CRF that has already been entered and submitted on to the database, the site should contact the C-STICH2 trial office so that the form can be checked out to them and an explanation of the errors entered.

Data reported on each CRF should be consistent with the source data or the discrepancies should be explained. If information is unknown, this must be clearly indicated on the CRF. Completed CRF's will be reviewed by the C-

STICH2 trial office for completeness. All missing and ambiguous data will be queried.

Data queries will be generated on a regular basis by C-STICH2 trial office staff and reported to the site for clarification within 28 days. The process of entering data on to the database itself forms a data quality check, as ranges are put in place to ensure that only viable data values can be input. It will be the responsibility of the Principal Investigator to ensure the accuracy of all data entered in the CRFs. These responsibilities may be delegated to an appropriate member of trial site staff. Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable trial-related procedures. The C-STICH2 trial Delegation Log will identify all those personnel with responsibilities for data collection.

Questionnaires completed remotely by the women will be received by the BCTU and will be transcribed directly onto the database. Given that these are patient reported outcomes, a data query process cannot be implemented.

CRFs may be amended and the versions updated by the C-STICH2 trial office, as appropriate, throughout the duration of the trial. Whilst this may not constitute a protocol amendment, new versions of the CRFs must be implemented by participating sites immediately on receipt.

12.5. **Data Security**

The security of the system is governed by the policies of the University of Birmingham. The University's Data Protection Policy and the Conditions of Use of Computing and Network Facilities set out the security arrangements under which sensitive data should be processed and stored. All studies at the University of Birmingham have to be registered with the Data Protection Officer and data held in accordance with the General Data Protection Regulations. The University will designate a Data Protection Officer upon registration of the study. The Study Centre has arrangements in place for the secure storage and processing of the study data which comply with the University of Birmingham policies.

The system incorporates the following security countermeasures:

- Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fireproof safe.
- Logical measures for access control and privilege management: including restricted accessibility, access controlled servers, separate storage of non-identifiable data etc.
- Network security measures: including site firewalls, antivirus software, separate secure network protected hosting etc.

- System Management: the system shall be developed by the BCTU Programming Team and will be implemented and maintained by the BCTU Programming Team.
- System Design: the system shall comprise of a database and a data entry application with firewalls, restricted access, encryption and role based security controls.
- Operational Processes: the data will be processed and stored within the Study Centre (University of Birmingham).
- Data processing: Statisticians will only have access to anonymised data.
- System Audit: The system shall benefit from the following internal/external audit arrangements:
    - Internal audit of the system
    - An annual IT risk assessment
- Data Protection Registration: The University of Birmingham has Data Protection Registration to cover the purposes of analysis and for the classes of data requested. The University's Data Protection Registration number is Z6195856.

12.6. **Archiving**

Archiving will be authorised by the BCTU on behalf of the Sponsor following submission of the end of trial report.

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g. signed ICFs, Investigator Site Files, participants' hospital notes, copies of CRFs) at their site are securely retained as per their NHS Trust policy, for at least 25 years after the completion of the trial.

Destruction of essential documents will require authorisation from the BCTU on behalf of the Sponsor.

13. **QUALITY CONTROL AND QUALITY ASSURANCE**

13.1. **Site Set-up and Initiation**

The CI is required to sign a BWCH CI agreement to document the expectations of both parties. The BWCH CI agreement document must be completed prior to participation. The CI is required to sign a Clinical Trials Task Delegation Log, which documents the agreements between the CI and BCTU. In addition, all local PIs will be asked to sign the necessary agreements including a Site Signature and Delegation log between the PI and the CTU and supply a current Curriculum Vitae (CV) and GCP certificate to BCTU. All members of the site research team are

required to sign the Site Signature and Delegation Log, which details which tasks have been delegated to them by the PI.

Prior to commencing recruitment, each recruiting site will undergo a process of initiation, either via a meeting or a teleconference, at which key members of the site research team are required to attend, covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data, and record keeping. Sites will be provided with an Investigator Site File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The BCTU trials team must be informed immediately of any change in the site research team.

13.2. **Monitoring**

There is always a need for monitoring to ensure safety of participants and the credibility of the data. Monitoring can be performed by visiting the trial site and by utilising centralised monitoring. A risk assessment will be performed to identify the risks and how these can be mitigated through both on-site and centralised. Findings generated from monitoring should be shared with local Research and Development (R&D) departments who may have plans to perform quality checks on the same trial.

13.3. **Onsite Monitoring**

Monitoring is carried out as required following the trial specific risk assessment and as documented in the monitoring plan. The monitoring plan should be approved by the Quality Assurance (QA) Manager before it is implemented. The number of sites to be monitored and the basis for selecting those sites for this trial we will specified in the trial monitoring plan.

Any monitoring activities will be reported to the trials team and any issues noted will be followed up to resolution. Additional on-site monitoring visits can also be triggered, for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of participant withdrawals or deviations. If a monitoring visit is required, the C-STICH2 trials team will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the C-STICH2 trial staff access to source documents as requested. The monitoring will be conducted by the quality assurance team of the sponsor.

13.4. **Central Monitoring**

Trial staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trial staff will check incoming ICFs for compliance with the protocol and CRFs for data consistency, missing data and timing. Sites will be sent DCFs requesting missing data or clarification of inconsistencies or discrepancies.

Sites will be requested to send in copies of signed ICFs for in-house review for all participants providing explicit consent. Source data can be requested for the purpose of central monitoring (e.g. for checking eligibility or endpoints). If such source data are requested, documents should be redacted and labelled with the participant's trial specific ID number. This will be detailed in the monitoring plan.

13.5. **Audit and Inspection**

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data and/or documents. The investigator will comply with these visits and any required follow up. Sites are also requested to notify BCTU of any relevant inspections.

13.6. **Notification of Serious Breaches**

The sponsor is responsible for notifying the Research Ethics Committee (REC) of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial. Sites are therefore requested to notify the C-STICH2 Trial Office of any suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trials Office is investigating whether or not a serious breach has occurred, sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the C-STICH2 specific committees and/or stakeholders (e.g., Trial Management Group, Trial Steering Committee, the Sponsor), and the REC. This includes reporting serious breaches of GCP and/or the trial protocol to the REC.

14. **END OF TRIAL DEFINITION**

The end of trial will be six months after the last data capture, based on the general health and PARCA-R questionnaire at two year follow-up, allowing for data collection and cleaning. The BCTU trial team will notify the main REC and Sponsor that the trial has ended and a summary of the clinical trial report will be provided within 12 months of the end of trial.

15. **STATISTICAL CONSIDERATIONS**

15.1. **Original sample Size for the RCT**

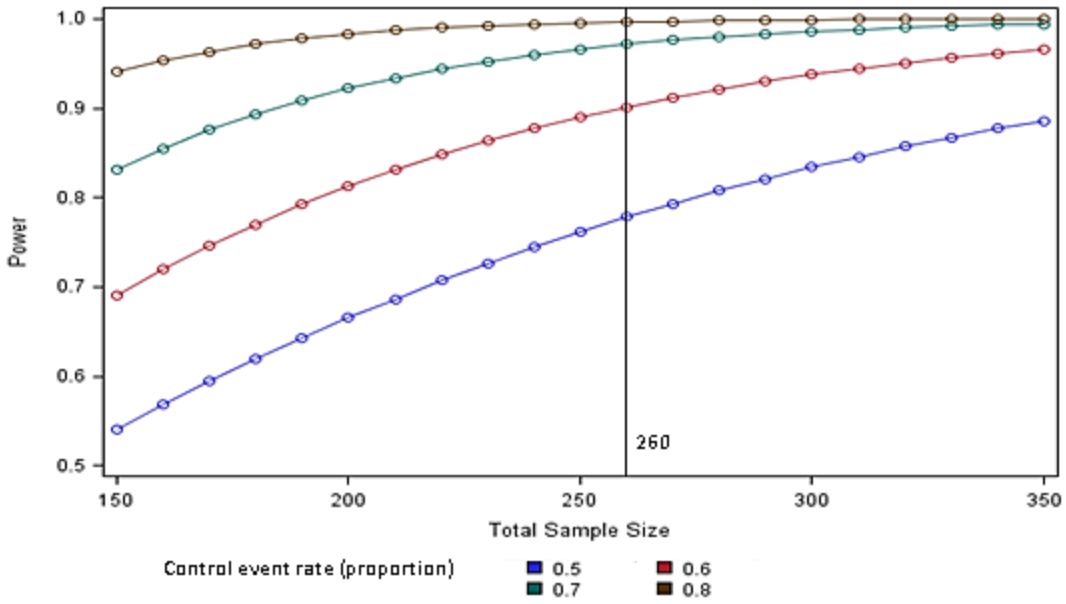
The sample size for the trial is informed by examination of the available evidence, with some allowance made for the fact that it is largely from small, non-randomised sources and likely to be biased. There is also recognition that mortality estimates in the expectant management group (control/usual care) are associated with a great amount of uncertainty and hence different scenarios have been produced.

The published literature that is available (as described in section 1) noted large effect sizes in favour of cervical cerclage: 67% relative reduction in the rate of death in the observational cohort (75% down to 25%) and a 38% relative reduction in the single, small, trial (71% down to 44%)[8]. We accept these effect sizes are likely to be exaggerated due to the poor quality of the studies and so have opted for a more conservative target difference of a 33% relative risk reduction from 60% mortality to 40%.

To enable us to have 90% power (p=0.05) to detect this difference would require 260 women in total (130 in each group). This size of difference would be more plausible than the results previously observed and would certainly be clinically meaningful but, we accept that smaller differences are also likely to be clinically important [12]. If the control group event rate is not as anticipated, 260 participants would give high level of power (at least 80%) in many scenarios particularly as the event rate approaches high levels (Figure 1). It is plausible the event rate may be very high as the chance of neonatal death approaches 100% in those presenting in early gestation between 16-22 weeks.

Loss to follow-up post-randomisation is anticipated to be low. If there are any withdrawals from the trial we will over-recruit to an equivalent amount to make sure we have 260 sets of data with primary outcome as a minimum.

Figure 1: Power curves assuming 33% relative reduction and control group event rates of 50%, 60%, 70% and 80%



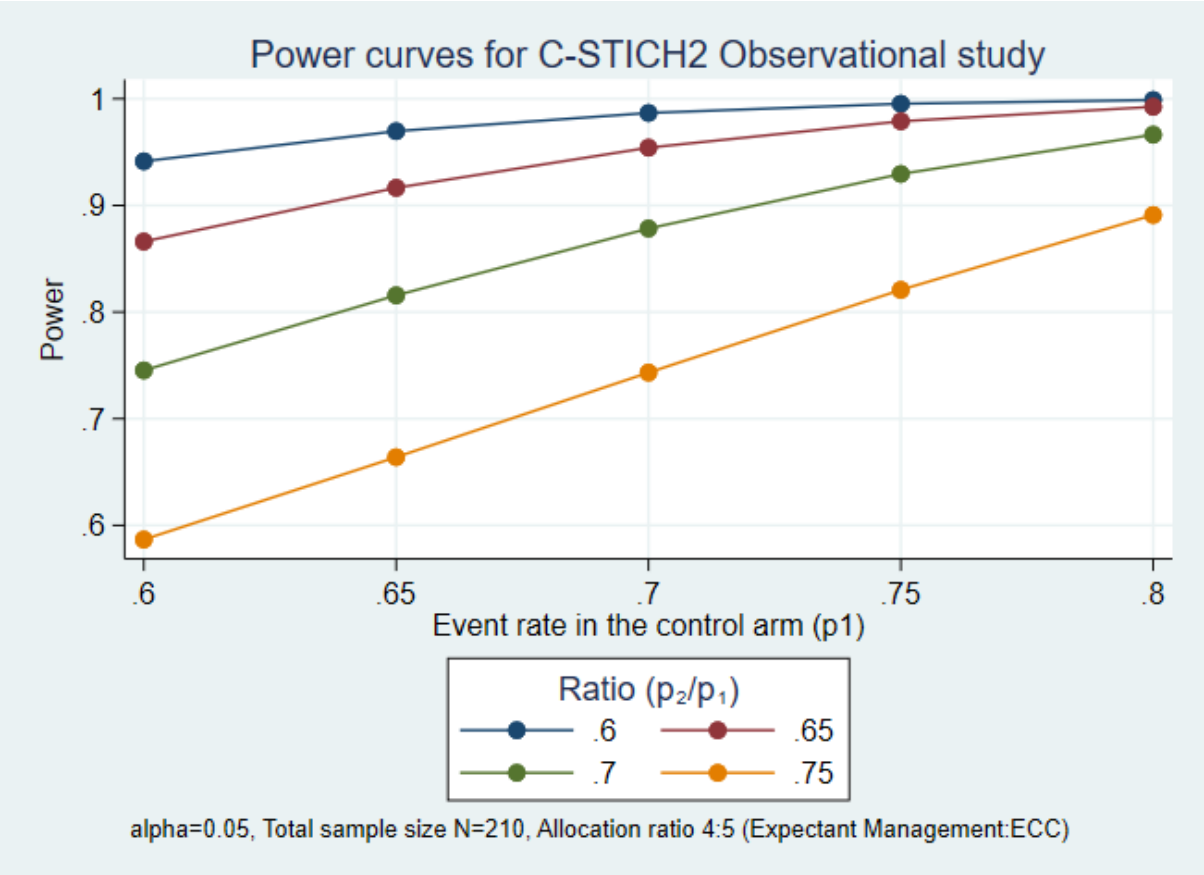
15.2. **Revised sample size following the pilot**

Following review of the internal pilot study and addition of the observational cohort study to the study design, a pragmatic approach has been taken to the final sample size. Assuming a recruitment rate of 5 women/per month to the observational cohort study, over a two year recruitment period, this will result in 120 women being recuited to this the observational cohort by the end of the study.

The final sample size for the C-STICH2 study has been revised based on current recruitment rates.

An additional 90 eligible women, have already been recuited into the minimal dataset of C-STICH2. Where the minimal datset contains data on the primary outcome of pregnancy loss and other key outcomes (section 8.3) If we combine these groups of women, we will have a total sample size of 210 women who were eligible for C-STICH2 but were not enrolled into the RCT. Assuming a recruitment ratio of 5:4 (cerclage: expectant management) a sample size of 210 will allow adequate power (>80%) for a range of effect sizes and control rates of pregnancy loss (Figure 2).

Figure 2: Power curves for the observational cohort study



15.3. **Analysis of Outcome Measures for the RCT**

A separate Statistical Analysis Plan (SAP) will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of these analyses is given below. The primary comparison groups will be composed of those allocated to ECC versus those allocated to expectant management. For all outcome measures, appropriate summary statistics will be presented by groups (e.g. frequencies and percentages for categorical, mean and standard deviation for normally distributed continuous and median and interquartile range for non-normal continuous outcomes). Treatment effects will be adjusted for the minimisation variables listed in section 6.4 where possible. No adjustment for multiple comparisons will be made.

15.3.1. Primary Outcome Measure

Relative risks and associated 95% confidence intervals will be generated using a mixed-effects log-binomial model regression model, adjusting for the minimisation variables listed in section 6.4. All minimisation variables will be treated as fixed effects, apart from site which will be included as a random effect. A chi-square test will be used to test the statistical significance (a two-sided p-value produced, with statistical significance determined at the 5% level) of the estimated treatment group parameter generated from the maximum likelihood estimates. All randomised participants will be included in this analysis and analysed in the treatment group to which they were randomised in the first instance, regardless of treatment compliance (intention-to-treat).

15.3.2. Secondary Outcome Measures

All dichotomous secondary outcomes will be analysed in the same fashion as the primary outcome. Time to event outcomes (e.g. time from conception to pregnancy end) will be presented using Kaplan Meier curves. Gestation at delivery, birth weight (adjusted for gestational age and sex) and output from PARCA-R evaluations at two years will be analysed using a mixed linear regression model, adjusting for the intervention group and the minimisation variables listed in section 6.4 (again, site will be included as a random effect). Count data (e.g. days on respiratory support) will be analysed descriptively using medians and interquartile ranges as the prevalence of such events is anticipated to be low. Regarding safety, the total number of patients experiencing SAEs will be given by intervention group along with a descriptive table of the events, and statistical significance will be determined by a chi-square test. Analysis populations for secondary outcomes (e.g. only in live births>=24 weeks) will be defined in the SAP.

15.3.3. Subgroup Analyses

Subgroup analyses will include the same variables used in the minimisation algorithm (see section 6.4), apart from the maternity unit, and in addition use of adjuvant treatments (i.e. progesterone, indomethacin, antibiotics) and cervical

dilatation (≤3cm, ≥4cm, fully dilated minimal cervix felt). Tests for statistical heterogeneity (e.g. by including the treatment group by subgroup interaction parameter in the regression model) will be performed prior to any examination of effect estimate within subgroups. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

15.3.4. Missing Data and Sensitivity Analyses

Every attempt will be made to collect full follow-up data on all study participants; it is thus anticipated that missing data will be minimal for the primary outcome. Participants with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. This will consist of simulating the missing responses using a multiple imputation approach. Full details will be included in the Statistical Analysis Plan.

15.4. **Analysis of Outcome Measures for the observational cohort study and minimal dataset**

A separate Statistical Analysis Plan (SAP) will be produced and will provide a comprehensive description of the planned statistical analyses for the observational cohort study and minimal dataset.

15.5. **Planned Interim Analysis**

Interim analyses of safety and efficacy for presentation to the independent DMC will take place during the study. The committee will meet prior to study commencement to agree the manner and timing of such analyses but this is likely to include the analysis of the primary and major secondary outcomes and full assessment of safety (SAEs) at least at annual intervals. Criteria for stopping or modifying the study based on this information will be ratified by the DMC. Details of the agreed plan will be written into the SAP. Further details of DMC arrangements are given in section 16.6.

15.6. **Planned Final Analyses**

The primary analysis for the study will occur once all participants have completed maternal and neonatal outcomes and the corresponding outcome data has been entered onto the study database and validated as being ready for analysis. The two year assessment data will be analysed separately.

16. TRIAL ORGANISATIONAL STRUCTURE

16.1. Funder

The National Institute for Health Research is funding the C-STICH2 trial through their Health Technology Assessment funding stream, which was awarded following a competitive two stage application and review process.

16.2. Sponsor

Birmingham Women's and Children's NHS Foundation Trust will act as sponsor for the C-STICH2 trial, taking overall responsibility for the initiation and management of the trial, and oversight of financing.

16.3. Coordinating Centre

Birmingham Clinical Trials Unit (BCTU) is responsible for providing all trial materials, including the trial folders containing printed materials. These will be supplied to each collaborating centre, after relevant R&D approval has been obtained. Additional supplies of any printed material can be obtained on request. BCTU will provide the central randomisation service and is responsible for collection and checking of data (including reports of SAEs thought to be due to trial interventions), for reporting of serious and unexpected adverse events to the Sponsor and/or the REC for analyses. BCTU will facilitate collaborating centres to resolve any local problems that may be encountered in trial participation.

16.4. Trial Management Group

The Trial Management Group (TMG) includes those individuals responsible for the day-to-day management of the trial, including the CI, senior statistician, trial statistician, team leader, senior trial manager, research fellow(s), data manager and qualitative researchers. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to, and to take appropriate action to safeguard participants and the quality of the trial itself. The TMG will meet monthly at face-to-face meetings.

16.5. Trial Steering Committee

The role of the Trial Steering Committee (TSC) is to provide the overall supervision of the trial. The TSC includes members who are independent of the investigators, their employing organisations, funders and sponsors. The TSC will operate in accordance with a trial specific charter. The TSC should monitor trial progress and conduct and provide advice on scientific credibility of the C-STICH2 trial. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC) or equivalent and ultimately carries the responsibility

for deciding whether a trial needs to be stopped on grounds of safety or efficacy, or substantially modified.

16.6. **Data Monitoring Committee**

An independent data-monitoring committee has been established to assess at intervals the progress of the study, the safety data, and the critical endpoints, and to recommend to the TSC whether to continue, modify, or stop the trial.

Data analyses will be supplied in confidence to the independent Data Monitoring Committee (DMC), which will be asked to give advice on whether the accumulated data from the trial and cohort study, together with the results from other relevant research, justifies the continuing recruitment of further participants. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. The charter will include terms of reference including those relating to the analysis at the end of the pilot and stopping guidelines.

The DMC will meet at least annually. If the trial continues past the pilot stage, the DMC will continue to meet at least annually until recruitment has finished and then meet yearly in the follow-up phase) unless there is a specific reason (e.g. safety concerns) to amend the schedule.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the Trial Steering Committee who will convey the findings of the DMC to the Trial Management Group, Sponsor and funders.

16.7. **Co-Investigator Group (CiG)**

The Co-investigator Group (CiG) is an extended TMG and will meet every six months initially, then less frequently to review progress, troubleshoot and plan strategically. The CIG consists of all members of the co-applicant group and all PPI representatives.

16.8. **Finance**

This is a commissioned call trial funded by the NIHR. The grant will be administered by the Sponsor. The Clinical Research Network will automatically adopt the C-STICH2 trial onto the NIHR portfolio, which will entitle the C-STICH2 trial to CRN support.

17. ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, 1964, amended by the 48th WMA General Assembly, Somerset West, Republic of South Africa, 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research, the applicable UK Statutory Instruments, (which include the General Data Protection Regulation) and the principles of GCP. The protocol will be submitted to and approved by the main REC prior to circulation.

Before any participants are enrolled into the trial, the PI at each site will obtain local R&D approval. Sites will not be permitted to enrol participants until written confirmation of R&D approval is received by the BCTU trials team.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

18. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the General Data Protection Regulation.

Participants will always be identified using their unique trial identification number, on the Case Report Form and correspondence between the BCTU. Women will give their explicit consent for the movement of their consent and randomisation form, giving permission for BCTU to be sent a copy. This will be used to perform in-house monitoring of the consent process and to facilitate follow-up at 2 years of age.

The Principal Investigator must maintain documents not for submission to BCTU (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, if participant confidentiality is protected.

BCTU will maintain the confidentiality of all participants' data and will not disclose information by which participants may be identified to any third party, other than

those directly involved in the treatment of the participant and organisations for which the participant has given explicit consent for data transfer. Representatives of the C-STICH2 trial team and sponsor may be required to have access to participant's notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times.

18.1. **Financial and other competing interests**

The Chief Investigator declares that there are no ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial. There are no commercial ties that require disclosure, which include any pharmaceutical, behaviour modification and/or technology company. Furthermore, there are no non-commercial potential conflicts (e.g. professional collaborations that may impact on academic promotion). It should be noted that at the time of writing the current version of the protocol, not all staff or sites have been identified. When this is the case, financial and other competing interest will be documented.

18.2. **Insurance and Indemnity**

This is a clinician-initiated trial. The Sponsor (the BWCNFT) holds the relevant insurance for Clinical Trials (negligent harm). Participants may be able to claim compensation, if they can prove that the BWCNFT has been negligent. However, as this clinical trial is being carried out in a hospital setting, NHS Trusts, NHS health Boards and Non-Trust Hospitals have a duty of care to the participants being treated. Compensation is only available via NHS indemnity in the event of clinical negligence being proven. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the CI, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office. There are no specific arrangements for compensation made in respect of any SAE occurring though participation in the trial, whether from the side effects listed, or others yet unforeseen.

Hospitals selected to participate in this trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary should be provided to BWCNFT, upon request.

19. **AMENDMENTS**

All amendments will be tracked in the 'Protocol Amendments' section of the protocol (section 0). The decision to amend the protocol and associated trial documentation will be initiated by the TMG. The Sponsor will be responsible for deciding whether an amendment is substantial or non-substantial. Substantive changes will be submitted to REC and HRA for approval. Once this has been received, R&D departments will be notified of the amendment, and requested to provide their approval. If no response

is received within 35 days, an assumption will be made that the site has no objection to the amendment and it will be implemented at the site.

20. **PUBLICATION POLICY**

Regular newsletters will keep collaborators informed of trial progress, and meetings will be held to report the progress of the trial and to address any problems encountered in the conduct of the trial. Results of this trial will be submitted for publication in a peer-reviewed journal. The manuscript will be prepared by the Trial Management Group who will be listed as individual authors. All contributors to the trial will be identified as the C-STICH2 Study Group with individual names and contribution listed as an appendix. Collaborating site teams will be acknowledged in the acknowledgement section of manuscripts with a list provided on the trial website. Trial participants will be able to access the final results of the trial via the trial website, which will contain a reference to the full paper and lay summary.

All publications/presentations using data from this trial to undertake original analyses will be submitted to the TMG for review before release. These must be submitted in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. On all publications, the authors must acknowledge that the trial was performed with the support of BWCNFT and acknowledge that the trial was funded by the National Institute for Health Research. To safeguard the scientific integrity of the trial, data from this trial will not be presented in public before the main results are published without the prior consent of the TMG.

21. QUALITATIVE PROCESS EVALUATION

Aim

- To qualitatively explore the feasibility, acceptability and appropriateness of the trial and intervention for women and healthcare professionals (HCPs)

Objectives

- With women: to explore their views and experiences of the recruitment approach, randomisation, barriers and facilitators to participation, intervention acceptability, and experiences of care pre- and post-intervention.
- With healthcare professionals: to explore their views and experiences of recruitment, randomisation, including perceived barriers and facilitators, equipoise, appropriateness and acceptability of the intervention, and perceptions of trial processes.

This qualitative process evaluation study is aligned with the MRC framework for evaluation of complex interventions [13].

The qualitative process evaluation completed in June 2020 and informed the next stages of the study, information on the processes utilised is included here for completeness.

Outcomes

The primary outcome of the qualitative process evolution is to explore the feasibility, acceptability and appropriateness of the trial and intervention for women and healthcare professionals (HCPs). This may include informing decision-making around progression to a full trial and study design and processes. In addition, the results may help to (a) inform improvements to NHS care for women presenting at 16+0 - 27+6 weeks, with premature cervical dilatation and exposed, unruptured fetal membranes; (b) inform future maternity guidelines.

Eligibility

Inclusion

- All women eligible for C-STICH2 randomised controlled trial and approached about the trial, irrespective if they agree to participate or not.
- All healthcare professionals caring for women at high risk of preterm birth and involved in the delivery of the C-STICH2 trial

- Those able and willing to give written, electronically completed or verbal (that is audio recorded) informed consent

Exclusion

- Women who would not be able to participate in an interview due to language barriers (interviews will be undertaken in English).

Participant identification and recruitment

Women will be approached to participate in an interview after they are approached to participate in the trial, whether they consent to the trial or not. This approach may be face to face and if they verbally consent to potentially taking part in an interview, they will be asked to provide their contact details to the recruiting clinician who will pass these details on to the qualitative research team. In addition, recruiting clinicians or research midwives will review their site specific screening logs and notes of all women approached about the trial. Where there is no documented evidence of discussion about the qualitative study or where women have asked to be contacted about the qualitative study at a later time the research midwives will follow up women with a letter specific to their decision about participating in the trial (e.g. decliner or randomised). The notes review and follow up letters will be sent within approximately 4 weeks of the approach about the trial. Women who have clearly declined participation in the qualitative study will not be contacted via letter.

HCPs will be approached directly by the qualitative research team after being identified from the delegation logs, through collaborator events and established clinical network. If they agree to participate they will be asked to provide written, electronically completed or verbal (that is audio recorded) informed consent to the qualitative research team.

Consent and withdrawal

Subsequent to consent to contact (following the initial approach), the research team will liaise with participants via telephone, SMS and/or email, to answer any questions about the research, confirm eligibility, and arrange an appropriate opportunity for an interview. Eligible participants will be invited to take time to consider participation carefully. It will be made clear that involvement in the study is voluntary and that they are free to withdraw up to two weeks after the interview without giving a reason and all audio recordings and transcript data will be destroyed. For those who decide to take part, participation instructions and appointment reminders will be sent via email/SMS or via phone ahead of each interview. For those who wish to participate via a phone/video conferencing interview a participant information leaflet and consent form will be sent via post/email ahead of the scheduled interview with instructions on how to complete the forms and return them to the research team.

written record of informed consent to participate will be sought wherever possible. However, for example, in cases where the study related paperwork has not been received, not fully completed, or there are issues around literacy then we will seek alternative forms of informed consent including electronically completed (e.g. electronic completion of the form and scanning/photo of the completed consent form returned) or verbal (e.g. where the consent form will be read out in full and audio recorded at the start of the interview). Informed consent (including written, electronically completed and/or verbal (that is audio recorded)) will include agreement to participate, demographic data collection, audio recorded dialogue of discussion, and anonymised data sharing. At the beginning of each audio recording, participants will be asked to verbally re-confirm consent. Were formal verbal informed consent is being sought at the start of a phone interview, then the audio recorder will be switched on and the consent form will be read out, and the participant asked to consent to each statement. Should the participant not consent to any of the statements then the interview will be terminated at that point having explained to that participant that data collection cannot continue, as they did not consent to participate.

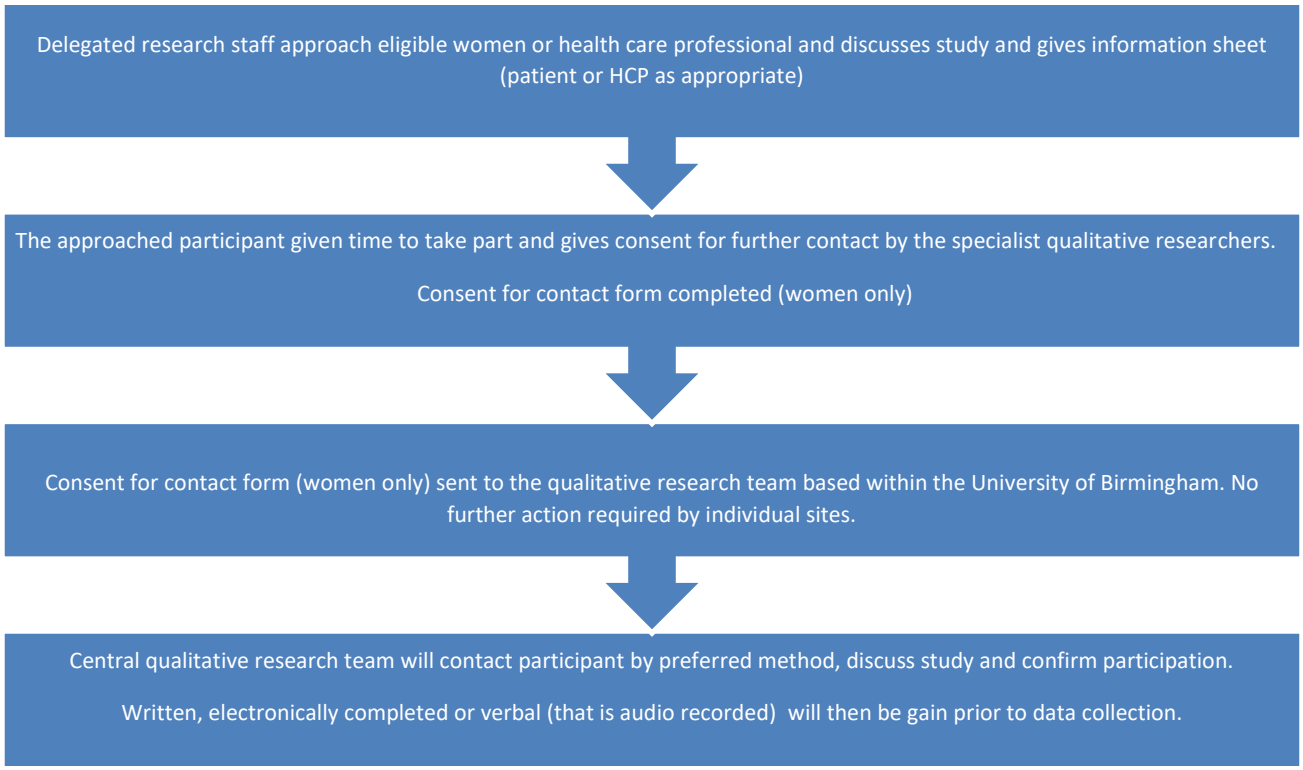


Figure 3: Qualitative interview process

Data collection

Participants who agree to be interviewed will be offered the choice as to whether the interview takes place in their own home (women), in a private room in the clinic where they were treated/work, at the university of Birmingham (if they are local to Birmingham) or via telephone/video conferencing (such as Skype/WhatsApp). For women, we will aim to conduct interviews within six to eight weeks of them being approached to participate (decliners) or being randomised (women who consent to participate). This will however remain flexible to accommodate the needs of the women.

A discussion guide to facilitate the interviews will be developed informed by existing literature (for example the domains proposed in the Theoretical Framework for Acceptability of Healthcare Interventions [14], patient and public involvement, and discussions within the C-STICH-2 team. Interviews will be conducted in a participant-focused manner allowing issues and perspectives important to participants to emerge naturally [15]. For women, interviews will explore their views and experiences of the recruitment approach, randomisation, barriers and facilitators to participation, intervention acceptability, and experiences of care pre- and post-intervention. For healthcare professionals, interviews will explore their views and experiences of recruitment, randomisation, including perceived barriers and facilitators, equipoise, appropriateness and acceptability of the intervention, and perceptions of trial processes.

Anticipated sample sizes

We aim to undertake semi-structured one to one interviews across the sites involved in the trial and will attempt to purposively recruit participants from the following groups (number of interviews per group provided in brackets):

a. women who decline to participate (n~5-7)
b. women randomised to the standard care treatment group (n~10-14)
c. women randomised to emergency cervical cerclage (ECC) treatment group (n~10-14)
d. senior clinicians involved in recruitment and randomisation (n~10-14)
e. midwives involved in the delivery of care to women who are approached to participate in the trial (n~10-14)

Based on recruitment projections for the trial, approximately 50 women will have been recruited and randomised during the 16 months of qualitative data collection. Our aim is therefore to interview roughly half of these women.

There will be up to 65 trial sites each with at least one senior clinician involved directly in participant recruitment and randomisation and numerous midwives providing care to women who are approached to participate, therefore the HCP pool to recruit for interview will be large.

From experience, we expect the final sample to include approximately 50-60 interviews (both women and HCPs) but the numbers will remain flexible to ensure that we collect sufficiently rich data to address the aim and objectives of the study.

Data Analysis

Interviews will be digitally-audio recorded, with data collection and initial analysis taking place iteratively [16]. Data collection will continue until the research team judge that the data and sample had sufficient depth and breadth to address the study aim [17]. Audio files will be transcribed clean verbatim by an external specialist transcription company and the framework approach [18] used to facilitate a systematic and flexible approach to the analysis.

Management of risk

There is potential that participants within this study, in particular the women, may be very distressed based on their experiences, potentially including the loss of the pregnancy. It will be clearly stated in the participant information sheet, by the person introducing the potential participant to the study, as well as being reiterated by the researcher at the beginning of the interview that participants are free to withdraw at any time up to two weeks after the data collection event without having to explain or justify their decision. All participants will self-select to take part. The welfare of the participants will always be placed ahead of the knowledge to be gained and emotionally distressing topics will be handled with sensitivity and sympathy and will follow the CSTICH-2 Interview Study Distress Pathway. The interviewer will also signpost the distressed participant towards services for additional support should this be appropriate. Information on support services is also provided in the participant information leaflet. We have sought PPI input to facilitate co-production and co-design of the study and all participant facing materials to ensure that they are appropriate.

If a participant raises issues about their care that the qualitative research team deem as potentially harmful to them (or others) then the researcher will advise them to contact their local Patient Advise and Liaison Service (PALS) (or equivalent) whose contact details are provided in the PIS. The lead for the qualitative sub-study, Dr Laura Jones, will also inform the CI, Dr Katie Morris. The CI, where appropriate, will ensure that the local unit PI is aware of the woman and potential concerns so that follow-up can be arranged if required. Should a participant have questions about their clinical care then the qualitative research team will advise the woman to contact her clinical team and/or her GP.

Nesting within CSTICH-2 Trial

Interview recruitment will start in parallel with the pilot trial with qualitative data collection for 16 months total. This will include feedback in real time to allow the TMG to be adaptive to any problems identified. The final analysis and write up will be undertaken between prior to the pilot review DMC meeting.

22. HEALTH ECONOMICS

If emergency cervical cerclage is shown to be an effective intervention in preventing early delivery of babies then it is likely that important cost implications will be seen for the health care sector. For example, the intervention may help to maintain the pregnancy for a longer period, which avoids miscarriage or preterm birth, but it may also instead lead to an increase in the number of cases of preterm birth.

Preterm birth is associated with high costs both in the short term (neonatal care) and longer term for instance, given the potential impact on neurological development which may lead to the child requiring special needs assistance through early childhood, schooling and even adulthood. Given this, the economic evaluation will take the perspective of the NHS and Personal Social Services (PSS) and as far as possible, depending on available data in the literature, will also be analysed from the societal perspective.

Resource use data will be collected to estimate the costs associated with the intervention of ECC. We shall therefore prospectively collect data on NHS resources from all participating centres for both arms of the trial and follow-up care.

The main resources to be monitored include:

(1) the procedure of emergency cervical cerclage (including surgery, admission, medication)

(2) the resource use associated with antenatal care in both arms of the trial including antenatal visits to clinic and GP and contacts with the health service that are related to the pregnancy and knock on costs associated with other medication and any other additional monitoring

(3) additional resources associated with preterm birth and neonatal medication as required

(4) duration of stay in neonatal units inpatient days of mother

(5) admissions after discharge

Information on unit costs or prices will then be required to attach to each resource item in order that an overall cost per mother/infant pair can be calculated. Cost data will be collected from two principal sources. First, the trial itself will provide the time (staff and resources such as disposable and equipment) and other resource use data to estimate the costs incurred with the intervention and for expectant management

and associated antenatal care. Costs associated with many resources used in routine antenatal care have been previously researched, therefore the main focus in the current study will be on the differences in resource use and interactions with the health service that occur between the two arms of the trial. We will not estimate costs for interventions that are the same in both arms, such as routine antenatal ultrasound scanning or routine antenatal care. Primary cost data for many of other required resources will be collected from the participating hospital sites. Where possible, other cost data, such as those of routine care, will be collected from routine sources, including Curtis 2017[19]and hospital finance departments. Many cost data are already available in recently published sources. A study to investigate the costs of different levels of neonatal intensive care has already been carried out and other cost studies with relevant costs and costs associated with preterm delivery are available to supplement these [20].

22.1. **Economic analysis**

The main components to the analysis will be a within-study analysis, but a model-based analysis beyond the end of the trial will also be considered.

22.2. **Within study analysis**

This will use only data collected within the trial and so, estimates of costs and benefits will therefore relate only to the initial period and assessment and the principal outcome of the trial at 7 days expressed in terms of major outcomes averted (MOA), where MOA represents the primary outcome.

Further analysis based on all data up to the infant reaching 2 years of age will also be carried out; the outcome of this second analysis will be based on the parent report and neurodevelopment at two years. If sufficient data are available based on a pragmatic literature search, and if deemed justified based on any difference in neurological assessment/report at the study outcome at two years it may be deemed appropriate to model beyond the end point of the trial with appropriate emphasis on the limitations given data availability and predictions from this point for the life of the child.

22.3. **Model Based Analysis Beyond Main Trial Outcome**

If there is no clinically detectable impact on outcomes as a result of this trial it may be deemed unnecessary to model beyond the outcome of the trial. However, if the intervention leads to an increase in preterm birth then it will be necessary to assess the cost effectiveness of the intervention in the longer term to ensure account is taken of adverse outcomes, such as cerebral palsy. Therefore, if deemed necessary based on the outcome of the trial, we will model the longer-term impact (potentially the lifetime impact) if data allow. Using data from a pragmatic literature review the longer term impact associated with cerebral palsy has been estimated in other studies. If available data allow, this analysis will be conducted both from the NHS and societal perspective. Given the skewness inherent in most cost data and the concern of economic analyses with mean costs, we shall use a bootstrapping

approach in order to calculate confidence intervals around the difference in mean costs. Initially, the base-case analysis for the within trial analysis will be framed in terms of cost-consequences, reporting data in a disaggregated manner on the incremental cost and the important consequences as assessed in the trial. An incremental economic analysis will be conducted on the primary outcome and other secondary outcomes. The results of these economic analyses will be presented using cost-effectiveness acceptability curves to reflect sampling variation and uncertainties in the appropriate threshold cost-effectiveness value. We shall also use both simple and probabilistic sensitivity analyses to explore the robustness of these results to plausible variations in key assumptions and variations in the analytical methods used, and to consider the broader issue of the generalisability of the results. For the longer term model based analysis, if feasible, appropriate discounting adjustments will be made to reflect this differential timing. The base-case analysis will follow both Treasury and NICE recommendations for public sector projects.

23. **MINIMAL DATASET**

All women whom are:

- Not eligible for the RCT or observational cohort study;
- Eligible but decline participation in the RCT and observational cohort;
- Eligible but are not approached in a timely fashion to obtain consent for the RCT or observational cohort

will contribute to the evidence collected within C-STICH2.

Each participating unit will complete an anonymised minimal dataset of all women presenting at the unit who are considered suitable for an emergency cerclage or who have an emergency cerclage. Baseline characteristics and the primary outcomes will be collected with no personal identifiers being collected by the trials unit.

This data set will inform the TMG of the accurate prevalence of the condition and the outcomes informing the pilot phase of the trial.

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