Cerclage after Caesarean: a randomised controlled trial to assess the optimal preventative management for preterm birth secondary to caesarean section damage (ABOVE)

PROTOCOL

version 1.0 dated 29/02/2024

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1. STUDY SUMMARY AND CONTACT DETAILS

1.1. Study Synopsis

Protocol Full title	Cerclage after Caesarean: a randomised controlled trial to assess the optimal preventative management for preterm birth secondary to caesarean section damage (ABOVE)
Protocol Short Title	ABOVE: Cerclage after Caesarean
Study Phase	Phase III Clinical Trial
Co-sponsors	King's College London (KCL) and Guy's and St Thomas' NHS Foundation Trust
Chief Investigator	Professor Andrew Shennan
REC number	*To be added following submission*
IRAS number	327879
ISRCTN	*To be registered before first participant is recruited*.
Medical condition under investigation	Mid-trimester loss and/or preterm birth after in-labour caesarean section.
Purpose of clinical trial	This trial will compare two standard interventions - transabdominal (TAC) or transvaginal cerclage (TVC) - in women who have experienced mid-trimester loss or spontaneous preterm birth (sPTB) after an in-labour caesarean section.
Primary objective	To assess the efficacy of TAC compared with conventional vaginally placed cerclage.
Secondary objective	To compare the efficacy of TACs placed before pregnancy with those placed in pregnancy.
Trial Design	Randomised Controlled Trial
Endpoints	Preterm delivery <30 weeks gestation
Sample Size	243 participants
Summary of eligibility criteria	Women willing and able to give informed consent, aged 16 or above, who have had a previous term caesarean section in established labour followed by a mid-trimester loss (>14 w) or preterm birth at less than 30 weeks' gestation.
Version and date of final protocol	1.0 29/02/2024

1.2. Contact details of sponsors and investigators

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1.3. Funder

This study has been funded by a joint Action Medical Research and Borne charity project grant: AMR Project Grant Reference: GN2967. Address: Action Medical Research, 5th Floor, 167-169 Great Portland Street, London, W1W 5PF.

1.4. Chief Investigator signature

The Chief Investigator and the R&D (sponsor office) have reviewed this protocol. The investigators agree to perform the investigations and to abide by this protocol. The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP, the UK Data Protection Act (2018), the Trust Information Governance Policy (or other local equivalent), the UK policy Framework for Health and Social Care research, the Sponsor's SOPs, and other regulatory requirements as amended.

Chief Investigator

Andrew Shennan

Signature Date

1.5. **Protocol version record**

Version Stage	Versions No	Version Date	Protocol updated & finalised by;	Detail the key protocol update
Current	1.0	29/02/2024	N/A - original protocol	N/A - original protocol

1.6. Glossary of terms and abbreviations

CS	Caesarean section
DMC	Data Monitoring Committee
EMCS	Emergency Caesarean Section
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
ISRCTN	International Standard Randomised Controlled Trials Number
MTL	Mid Trimester Loss
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIS	Participant Information Sheet
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
sPTB	Spontaneous Preterm Birth
SSI	Site Specific Information
TAC	Transabdominal Cerclage
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TVC	Transvaginal Cerclage

2. INTRODUCTION

Preterm birth is the leading cause of neonatal mortality and morbidity worldwide. This has significant repercussions for individuals and their families and the economic costs to society are considerable (£1.24 billion in the UK)[1]. A significant association between in-labour, or emergency caesarean section (EMCS), at term and mid-trimester loss (MTL) or spontaneous preterm birth (sPTB) in subsequent pregnancies has been reported in recent years, with a 6-fold increased risk of sPTB following a full dilatation emergency caesarean section[2]. More worrying is the high risk of a recurrent sPTB in this group of women[2,3]. Nineteen percent of deliveries in England are by EMCS (n=103,684/year), with 6% estimated to be at full dilatation (FDCS). Our recent study[4] reported a relative risk of recurrent sPTB <37 weeks of 2.7 for all first stage EMCS, and 3.1 for FDCS, compared with women with a prior sPTB and no previous in-labour EMCS: absolute risk > 50%4. This risk is further increased when MTL is included (RR 5.65).

The mechanisms behind this are unknown but are likely to be related to cervical damage at the time of in-labour caesarean section (CS). The uterine incision may be made inadvertently too low including effaced cervical tissue as opposed to uterine tissue. This may lead to damage to the proximal cervix resulting in incompetence in future pregnancies[5]. This damage may also be influenced by suture material at the time of caesarean section, the healing process and incidence of post-operative infection. Treatment modalities to reduce sPTB are limited but include cervical cerclage/suture insertion[6]. Three types can be placed prophylactically at differing sites: a vaginally placed low or high cervical suture (known as transvaginal cerclages - TVCs) sited during pregnancy or a transabdominal suture, placed at the level of the internal os and requiring laparotomy/laparoscopy (Figure 1). Transabdominal cerclages (TACs) are currently reserved for women who have had a failed vaginally placed cerclage and are often inserted prior to pregnancy[7].

TVCs are widely used and effective at preventing sPTB in high-risk women[7]. However, retrospective studies show that they may not be as effective (ten-fold less) in women who have had a sPTB following an in-labour CS, compared to other high-risk groups[3]. Conversely, TAC has a success rate of >90% in high-risk women[8]. They may be a more effective treatment option in these women, due to the fact the suture is positioned higher in the cervix, above the area of previous scar tissue and likely damage. Women with a history of preterm birth and pregnancy loss report having a TAC in place reassuring[9].

3. PATIENT AND PUBLIC INVOLVEMENT

The trial proposal was presented at a meeting (December 2021) of our Guy's and St Thomas' NHS Foundation Trust, NIHR recognised, PTB Patient and Public Involvement (PPI) group, who considered the study to be "important", "needed", "we are excited about it". They were also asked (by email in April 2023) to review draft participant information sheets and consent forms, which were amended accordingly. In May 2023, we also asked for their opinion on whether about information in the PIS about storage of ultrasound scan pictures was sufficient, or whether separate consent would be necessary. Only one PPI contributor replied, who felt separate consent was not necessary. The PPI group have been kept informed on the progress of the study, will be consulted regularly throughout the project to advise on recruitment strategies and any amendments to the protocol or participant facing documents. They will also help to disseminate results via their social media networks. The Trial Steering Committee will also include a PPI representative.

4. TRIAL OBJECTIVES AND PURPOSE

The purpose of this trial is to compare two standard interventions, transvaginal cerclage (TVC) and transabdominal cerclage (TAC), to find out whether one is better than the other in preventing mid-trimester pregnancy loss (late miscarriage) or preterm birth in women who have had a previous caesarean section in labour.

We will also compare the pregnancy outcomes in women who had a TAC placed prior to pregnancy with those where a TAC was placed in early pregnancy. This will help us to determine whether women should be advised to have a TAC before pregnancy, rather than waiting until they are pregnant.

5. TRIAL DESIGN

5.1. Trial design

ABOVE is a multicentre RCT comparing TAC or TVC as a preventative strategy for sPTB in women with history of an in-labour CS and subsequent MTL (between 14^{+0}-23^{+6} weeks) or sPTB (<30 weeks). Participants will be allocated to one of two groups - Group A (already pregnant) and Group B (planning a pregnancy) - and randomised 1:1 to TAC or TVC within each group. It is important to separately evaluate pre-conception and in-pregnancy TACs. The suture can be placed higher pre-conception and this may provide

better support around scar weakness. Therefore, the trial is separately powered for these 2 groups, and will require complete data from 160 participants (80 in Group A, 80 in Group B). Recruitment will continue for 18 months.

5.2. Outcome measures

5.2.1. Primary outcome

The primary outcome is the occurrence of mid-trimester pregnancy loss or spontaneous preterm birth before 30 weeks of gestation.

5.2.2. Secondary outcomes

Maternal

- Admission to hospital for symptoms of threatened preterm labour
- Administration of antenatal corticosteroids for fetal lung maturation
- Administration of magnesium sulphate for fetal celebral protection.
- Transfer to other hospitals for neonatal cot availability (in-utero transfer)
- Time between intervention and delivery
- Requirement for additional emergency/rescue cerclage
- Serious complications occurring as a result of trial intervention: bladder injury, bowel injury, intraoperative rupture of membranes, cervical tear, hysterectomy
- Maternal sepsis
- Admission to ITU
- Maternal death

Neonatal

- Gestation at birth
- Birthweight
- Apgar scores (if available)
- Days before discharge home (up to 28 days)
- Admission to neonatal unit
- Neonatal infection
- In utero fetal death after 14 weeks
- Stillbirth
- Neonatal death

5.3. Participant selection and recruitment

Potential participants will be identified from women referred to obstetricians or specialist preterm birth services at participating sites. Eligible potential participants will be initially approached by clinicians when they attend for pre-pregnancy counselling or specialist preterm service appointments. They will be given verbal information about the study. If willing, they will be contacted by the local research team, which may include attending clinicians and/or research midwives, who will provide the written information sheet and the opportunity to ask questions. Potential participants will be given as long as they need to consider taking part, and will be informed that if they wish to proceed, they must decide within a timeframe that will allow the arrangement of the allocated intervention to be carried out before they are 14 weeks pregnant. If a potential participant does not speak or understand English, a professional interpreter will be utilised to ensure the participant is able to provide fully informed consent.

Group A: (in pregnancy recruitment): eligible participants will be referred by clinical staff after pregnancy booking e.g., first appointment with preterm specialist and will be contacted soon afterwards by clinical research midwives.

Group B: (pre-conception recruitment): eligible participants will be identified by referral (with the woman's permission) to the research team by clinical staff following a MTL or sPTB. These potential participants will then be approached by research midwives shortly after their NHS bereavement or post-partum debriefing consultant appointment, which is usually carried out six weeks after the event, or preconception counselling appointment which may happen at any time before a future pregnancy.

5.4. Participant inclusion criteria

Women will be eligible for the trial if they:

- are willing and able to give informed consent.
- are aged 16 or above.
- have had a previous in-labour caesarean section (between 4 cm and 10 cm (fully) dilated) followed by a MTL (>14 w) or preterm birth (<30 weeks).
- are pregnant, but will be less than 14^{+0} weeks' gestation at time of allocated intervention (Group A) **OR**
- are not yet pregnant but are considering a further pregnancy (Group B).

5.5. Participant exclusion criteria

Potential participants will not be eligible for the trial if they:

- are more than 14^{+0} weeks pregnant at time of randomisation (as insertion of TAC is associated with higher risk beyond this gestation),
- already have a cerclage or (Arabin) pessary *in situ,*
- are not planning another pregnancy,
- have a history of preterm birth (spontaneous/iatrogenic) prior to the in-labour caesarean section or
- are pregnant and expecting more than one baby (multiple pregnancy).

5.6. Randomisation procedures

Following written informed consent, participants (in either Group) will be randomised (1:1) to either TAC or TVC using a computer-generated randomisation procedure incorporated within the ABOVE trial database. Recruiters and trial co-ordinators will not have access to the randomisation sequence. Due to the nature of the interventions, the study is not blinded to the care providers or participants; they will be informed at time of recruitment to which arm they have been randomised.

5.7. Masking and other measures to avoid bias

5.7.1. *Masking*

Due to the nature of the interventions being evaluated it is not possible to conduct a double or single blinded trial, and both participants, clinicians and researchers will be aware of trial intervention.

5.7.2. *Other measures taken to minimise / avoid bias*

In order to ensure a balance between groups, randomisation will take account of whether the participant's previous in-labour CS was carried out at 4-9cm or at full dilatation (minimisation). This is because it is currently believed that a CS at full dilatation is likely to be more damaging than one carried out earlier in labour. If a potential participant is unsure of her cervical dilatation at previous in-labour CS, further details will be sought from the hospital where the operation took place, and if uncertainty remains a decision will be made within the study team as to which category she should be placed for the purposes of minimisation, before randomisation.

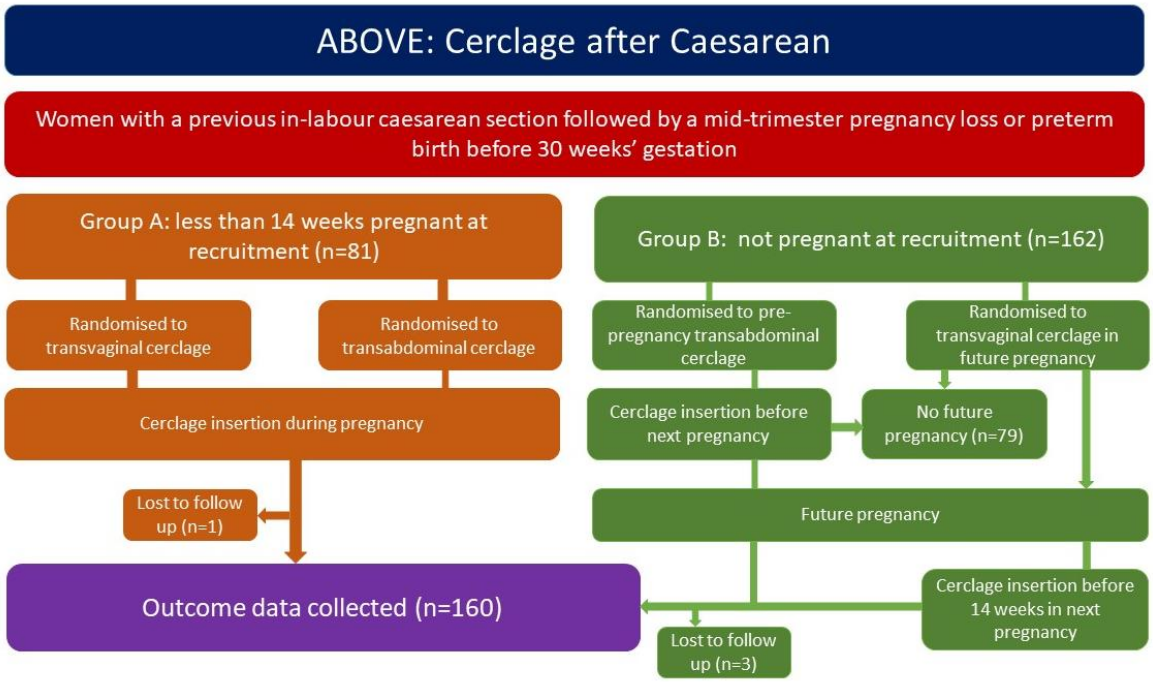
5.8. Schedule of assessments

Following randomisation, the allocated procedure will be arranged. Participants in Group A will have the cerclage (TAC or TVC) inserted prior to 14 weeks' gestation. Group B participants allocated to TAC will have the procedure placed before their next pregnancy and those allocated to TVC will have it placed during their next pregnancy before 14 weeks' gestation. TACs are performed as an open or laparoscopic procedure under either regional or general anaesthetic, requiring inpatient stay of up to 3 days. TVCs will be performed at the participant's local maternity unit with the insertion technique and anaesthesia according to clinician's discretion and local practices. TACs will usually remain in-situ (to support any future pregnancies) while TVCs are removed at around 37 weeks' gestation. TACs are more specialised procedures and so they may be carried out in designated specialist units, as per local practice. The timeframe between randomisation and study procedure is flexible from site to site, depending on theatre list availability, although all procedures must be carried out before the participant is 14 weeks' pregnant.

5.9. Follow up procedures

There are no trial specific follow up procedures. All other pregnancy care and special preterm prevention surveillance will continue according to local protocols. Data on clinical care and pregnancy outcomes will be collected from participants' maternity records.

5.10. Trial Flowchart



(n= number of participants)

6. END OF STUDY DEFINITION

In order to allow time for collection of outcome data and analysis, the end of study will be six months after the expected date of delivery of the last participant recruited.

7. ASSESSMENT OF SAFETY

7.1. Participant safety measures

Pregnant participants in this study will remain under the care of their local maternity care provider who will monitor their pregnancy according to local practice. Participants in Group B, who are not yet pregnant, will be advised to contact their local GP and/or healthcare providers if they become unwell or experience any complications following the trial intervention. All participants will be advised to inform their local Principal Investigate of any adverse events, who will be responsible for ensuring these are recorded

locally and reported to the Chief Investigator. The Chief Investigator is then responsible for reporting events to the regulators/R&D as the sponsor office.

7.2. Definition of serious adverse events (SAEs) in this study

The definition of a Serious Adverse Event (SAE) in this study is an event that:

- Results in death
- Is life-threatening
- Required hospitalisation or prolongation of existing hospitalisation, excluding admission for birth or unrelated pregnancy condition.
- Results in persistent or significant disability or incapacity
- Is otherwise considered medically significant by the Principal Investigator.

7.3. Reporting of serious adverse events (SAEs)

When an SAE is ***related*** (that is, it resulted from administration of any of the research procedures), to the study procedures and is an ***unexpected*** occurrence (that is, the type of event is not listed in the protocol as an expected occurrence), the SAE, must be reported immediately upon knowledge of the event to R&D and always within 24 hours. A note must be put in the case report form (CRF) and on the participants medical notes if they are patients.

All serious adverse events that are to be reported to R&D must be signed and dated and completed by the Chief Investigator.

If SAE/AE occurs that does not require immediate reporting, this should be recorded in the study site file and reported to GSTT when copied into the Annual Progress Report.

7.4. SAEs that are expected to occur during this study

SAEs that are expected to occur during this study, and therefore do not require reporting are:

- Any hospitalisation relating to birth or unrelated pregnancy condition.
- All events listed as secondary outcomes in Section 5.2.2 ***except*** *(i.e. these events need reporting)*:
    - Serious complications occurring as a result of trial intervention: bladder injury, bowel injury, intraoperative rupture of membranes, cervical tear, hysterectomy
    - Maternal sepsis

- Maternal admission to ITU
- Maternal death

7.5. Trial Steering Committee (TSC)

The role of the Trial Steering Committee (TSC) is to provide the overall supervision of the study. The TSC will monitor the progress of the study and conduct and advise on its scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the DMC and ultimately carries the responsibility for deciding whether the trial needs to be stopped on the grounds of safety or efficacy. The TSC will consist of an independent chair and at least two other independent members (not involved in study recruitment and not employed by any organisation directly involved in study conduct. A representative from our dedicated preterm birth studies Patient Public Involvement group will be invited to participate. The first meeting will take place 6 months after trial start date; frequency will be decided at the first meeting (at least annually).

7.6. Data Monitoring Committee (DMC)

The Data Monitoring Committee (DMC) will be convened to ensure the wellbeing of study participants. The committee will periodically review study progress and outcomes as well as reports of serious adverse events (SAEs). The DMC will, if appropriate, make recommendations regarding the continuance of the study or modification of the study protocol. The timings and content of the DMC reviews will be detailed in a DMC charter which will be agreed at its first meeting. The DMC will meet 3 months following study commencement/recruitment of the first participant; frequency of meeting will be decided at the first meeting.

7.7. Ethics & regulatory approvals

The study requires regulatory approval from the following bodies: NHS REC [*state the name and address of the committee*] Favourable Opinion and HRA Approval. Before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that the appropriate regulatory approvals have been issued, and NHS Confirmations of Capacity and Capability and Sponsor green lights are in place.

For any amendments to the study, the Chief Investigator or designee, in agreement with the Sponsor, will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D

departments as well as the study delivery team) to confirm ongoing Capacity and Capability for the study.

All correspondence with the Sponsor, REC and HRA will be retained. The Chief Investigator will notify the Sponsor and REC of the end of the study.

7.8. Ethics Safety Reporting

Reports of related and unexpected SAEs should be submitted to the Main REC within 15 days of the Chief Investigator becoming aware of the event, using the NRES template (see Appendix #.# below for detailed reporting instructions).

The forms should be completed in typescript and signed by the Chief Investigator. The main REC will acknowledge receipt of safety reports within 30 days. A copy of the SAE notification and acknowledgement receipt should be sent to the R&D@gstt.nhs.uk and stored in the TMF/Site file.

8. COMPLIANCE AND WITHDRAWAL

8.1. Participant compliance

The trial interventions (different cerclages) are one-off procedures. If a participant changes her mind about going ahead with the trial intervention after randomisation, we will confirm whether or not the participant is happy for any data already collected to be kept and used e.g., in intention to treat analysis.

8.2. Withdrawal / dropout of participants

Participants may withdraw from the trial without it altering their ongoing care. This option will be discussed at the time of consent and they will be told that withdrawal at any time during the study would not affect her clinical care. If they choose to withdraw data that has already been collected about them will be retained. Participants will be informed of this in the PIS. Efforts will be made to replace withdrawn participants with others within the timeframe of the study.

8.3. Protocol compliance

A Protocol deviation is usually an unintended departure from the expected conduct of the study protocol/SOPs, which does not need to be reported to the Sponsor. The CI will monitor protocol deviations and list them in a deviation log /include a file note in the TMF/Site file where applicable.

Significant deviations to the protocol or deviations which are found to frequently recur are not acceptable and need to be assessed by the CI to see if an amendment to the Protocol is required. These will require reporting to the Sponsor and action taken through Corrective and preventative Actions (CAPA).

A 'serious breach' is defined as a breach likely to effect to a significant degree:

- the safety or physical or mental integrity of the participants of the trial;
- The scientific value of the trial.

The CI and Sponsor must be notified immediately of a serious breach. The Breach must be reported to the REC Committee with the Sponsor in copy within 7 calendar days of the breach being confirmed as serious.

9. DATA

9.1. Data to be collected

Data will collected by attending clinician or research midwives and includes: ***at randomisation*** - participant background: demographic characteristics, risk factors, obstetric history; ***before pregnancy*** trial intervention procedure (Group B – TAC); ***during pregnancy*** - trial intervention procedures (Group A - TVC or TAC, Group B – TVC); clinical care: preterm surveillance methods and test results, e.g. infection screening, cervical length measurements, predictive biomarker tests, concomitant treatments; ***after pregnancy*** - outcomes: e.g. gestation at delivery, infection, admission to ITU (mother) and/or neonatal unit (baby).

The data collected will allow us to evaluate the effectiveness of the interventions on preventing poor outcomes, whether there are differences between women from different groups (demographic characteristics and risk factors) and whether treatment effects are compounded by other variables, such as intensity of preterm surveillance and concomitant treatments.

9.2. Data handling and record keeping

Data will be stored on the ABOVE Trial Database, which is hosted within the already established PCN Database (www.medscinet.net/ukpcn). This is a secure web-based platform containing standardised clinical information regarding women at high risk of sPTB[9]. MedSciNet is a Stockholm based company specialising in design and development of web applications and online database systems for clinical trials and studies, quality registries, medical bio-banks, and other solutions within the field of academic medicine.

They support many research organisations, groups and universities throughout the world, to achieve the benefits of web-based electronic data capture which include significant cost savings, as well as time, efficiency, and quality gains. The databases are very clear and simple to use, and predefined validation rules and data monitoring facility help to ensure accurate data entry. For details regarding the security of the Database, please refer to MedSciNet document: "Implementation and operation of MedSciNet's database applications for Medical Studies and Registers" (Appendix #.#). The Information Governance Department of Guy's & St Thomas' NHS Foundation Trust have reviewed and approved the security of the Database. A Data Protection Impact Assessment (DPIA) was carried out in June 2021 in collaboration with the KCL Information Compliance department.

9.3. Data retention

Any data relating to pregnancy care is required to be stored for at least 25 years. At the end of the study, pseudonymised research data will be locked and downloaded from the ABOVE database, saved in a read only format and archived according to Sponsor requirements (with Iron Mountain). Copies will also be kept on KCL Sharepoint. A file note will be placed in the Investigator Site File detailing the location of electronic data. Data will not be retained for use by other researchers (in a repository). This is because it will be impossible to adequately anonymise it due to the rarity of the condition and the small number of participants that will be recruited per site.

9.4. Data sharing

The data will not be shared with third parties, other than MedScinet, who are the company hosting the database. MedScinet servers are based in Sweden. All research data (pseudonymised) will be directly input into the ABOVE study database, as outlined above. Participant identifiers (identifiable data) are input directly by authorised local site users and kept on a secure separate but linked Medscinet "Patient Details" database, which is only accessible to authorised site users and the PCN Database Project Manager for providing user access and assistance in resolving queries.

Pseudonymised data for analysis will be exported in Excel format and stored onto a secure KCL Sharepoint site which is only accessible to authorised members of the study team.

9.5. Personal data breaches

GDPR broadly defines personal data breaches as a security incident that has affected the confidentiality, integrity or availability of personal data. In short, there will be a personal data breach whenever any personal data is lost, destroyed, corrupted or disclosed; if someone accesses the data or passes it on without proper authorisation; or if the data is made unavailable, for example, when it has been encrypted by ransomware, or accidentally lost or destroyed.

Personal data breaches must be immediately reported to the Sponsor/data controllers and to the Data Protection Officer/IG Department of the site that incurred the breach. The following information must be provided to assess the full risk/impact of the breach: full details as to the nature of the breach, an indication as to the volume of material involved, and the sensitivity of the breach (and any timeframes that apply), steps that have been taken to mitigate the risk (trying to retrieve the data asking third parties to delete information that was sent to them in error).

Sites will additionally follow their Trust incident reporting mechanisms such as datix and will document this within their TMF/ISFs in the form of a file note provided by the Sponsor with corrective and preventative measures addressed.

The Sponsor/Data Controller will determine whether the breach meets the definition of a serious breach and warrants reporting to the regulators including the ICO https://ico.org.uk/for-organisations/report-a-breach/personal-data-breach-assessment/.

10.MONITORING AND AUDITING

The Chief Investigator will be responsible for the ongoing management of the study. The Sponsor will monitor and conduct audits on a selection of studies in its clinical research portfolio. Monitoring and auditing will be conducted in accordance with the UK Policy Framework for Health and Social Care and in accordance with the Sponsor's monitoring and audit procedures.

The completeness and quality of the data will be monitored by the clinical fellow and study co-ordinator, overseen by the trial co-investigators. Medscinet databases have an inbuilt data monitoring and query resolution system, with complete audit trail. Site

researchers will be required to complete training before being given access to the live database.

10.1. Study Management Group

Study site meetings will be held approximately every two months (with video conferencing where required). All researchers and clinicians affiliated with the project will be invited to participate in these meetings which will allow discussion of all aspects of the project and the timely addressing of issues as they arise. The Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) will also provide monitoring and oversight for the good conduct of the study.

10.2. Study Coordinating Centre

The trial coordinating centre will be the Department of Women and Children's Health, Kings College London, where the study coordinator will be based. The Department of Women and Children's Health will be responsible for statistical analysis, servicing both the DMC and the Trial Steering Committee (TSC) and, in collaboration with the Principal Investigators, study coordinator and local Research Midwives/Nurses, for the day to day running of the study including recruitment of sites and training of staff.

11.STATISTICAL CONSIDERATIONS

11.1. Power calculation

We have based our sample size estimation on data from an observational study, performed by our group, that showed TAC to have a relative risk reduction of 67% for PTB <30 weeks compared to TVC in this high-risk cohort of women (unpublished data). A total of 40 women in each intervention group (TAC/TVC) is required for 80% power, at 5% significance level, to show a significant difference between the two groups. This would equate to a total of 160 women in the study; 40 x group TVC vs. 40 x TAC in both groups: Group A (in pregnancy) and Group B (prior to pregnancy). The recruitment target takes into account a potential drop-out rate of 50% of Group B participants who may not have a subsequent pregnancy after randomisation; as informed by the MAVRIC trial[8]. This power calculation has been calculated based on two arms of the trial (TVC vs TAC) and therefore, will allow sufficient power to detect a difference between TVC and TAC in each of the two groups.

11.2. Feasibility

In order to achieve 80 participants with complete data for analysis in each group, we estimate a total recruitment target of 243 is required (as per below):

Group	Target recruitment	Allowing for missing data	Comment
A (pregnant)	81	1	1-2% lost to follow up (*based on previous studies*)
B (not pregnant)	162	3	1-2% lost to follow up
		79	~50% pregnancy not completed within timeframe of this study.
Total	243		

Following a call for Expressions of Interest to members of the UK Preterm Clinical Network, 25 sites have confirmed they wish to participate. Ten of these are large tertiary hospitals and 15 are smaller hospitals. We estimate that the large tertiary hospitals will be able to approach 1 potential Group A participant and 2 potential Group B participants per month. We estimate the smaller hospitals to approach half this number. As potential participants will have experienced a mid-trimester loss or very preterm birth, they may be reluctant to be randomised, having heard, anecdotally, that TAC may be a more effective intervention. Therefore, of the number approached, we anticipate only 30% will consent to randomisation. Based on these estimates (detailed below) we expect to achieve our recruitment target within 18 months.

Type of site	Group A (pregnant)		Group B (not pregnant)	
	Approach	Consent	Approach	Consent
Tertiary hospitals (x 10)	10	3	20	6
Smaller hospitals (x 15)	5	1.5	10	3
Total per month	15	4.5	36	9
x 18 months		81		162

11.3. Analysis plan

A data analysis plan will be prepared prior to commencement of study recruitment. Analysis will be carried out using statistical software packages, e.g. Stata and SPSS. Odds ratios and risk differences, leading to a number needed to treat, if appropriate, according

to CONSORT guidelines, will be calculated. A subgroup analysis will be carried out according to other risk factors for preterm birth other than in-labour CS. The primary analyses will be by modified intention-to-treat for the pre-conception trial arms. The modification will take in to account the participants who do not conceive post-randomisation. A TVC will not be inserted in a non-pregnant patient (in line with standard clinical care) and therefore these participants will be removed from the trial, at the end of the 18 month recruitment period, to ensure that the analysis remains clinically valid. Subgroup analysis will be carried out to explore differences in demographic characteristics, risk profiles, hospital type (e.g. district general hospital, tertiary/teaching hospital) and geographical location.

11.4. Trial stopping rules

The ABOVE trial may be prematurely discontinued by the Sponsor, Chief Investigator or Regulatory Authority on the basis of new safety information or for other reasons given by the DMEC/TSC regulatory authority or ethics committee concerned. If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected. The Competent Authority and Research Ethics Committee will be informed within 15 days of the early termination of the trial.

12. PEER REVIEW

This study was peer reviewed through the funding application process.

13. FINANCING

This study has been funded by a three year joint Action Medical Research and Borne charity project grant: AMR Project Grant Reference: GN2967, awarded on 12th January 2023. Following award set up and contracting the official start date of the grant was 1st May 2023. As a period of more than six months has been required for trial set up, a no-cost extension will be sought to cover the 36 month timeframe.

14. INSURANCE AND INDEMNITY

The study is co-sponsored by King's College London (KCL) and Guys and St Thomas' NHS Foundation Trust (GSTT). The sponsors will, at all times, maintain adequate insurance in relation to the study. KCL through its' own professional indemnity (Clinical Trials) & no-fault compensation and the GSTT having a duty of care to patients via NHS indemnity

cover, in respect of any claims arising as a result of negligence by its employees, brought by or on behalf of a study participant.

15.DATA CONTROLLER

Guy's and St Thomas' NHS Foundation Trust (GSTFT) and King's College London (KCL) are co-sponsors of this research project and have shared Data Controller responsibilities. Where Personal Data is disclosed by GSTFT to KCL or vice versa, directly or indirectly to satisfy the requirements of the Protocol, or for the purpose of monitoring or reporting adverse events, or in relation to a claim or proceeding brought by a Participant in connection with the Trial, KCL and GSTFT agree to comply with the obligations placed on a Controller by the Data Protection Legislation. This is not limited to, but includes, being responsible for and able to demonstrate compliance with the principles relating to Processing of Personal Data (Article 5 UK GDPR).

GSTFT and KCL have outlined their Data Controller to Controller arrangements in an overarching Master Data Sharing Agreement which sets out the principles of data sharing in accordance with UK GDPR, regulatory and statutory laws. GSTFT and KCL have agreed to the mutual study specific Joint Controller data sharing template which details their individual roles and responsibilities at a study level.

16.INTELLECTUAL PROPERTY

This research is evaluating two standard interventions already used in practice and therefore is unlikely to lead to the generation of intellectual property.

17.REPORTING AND DISSEMINATION

Results of the study will be reported and disseminated at national and international conferences and in peer-reviewed scientific journals. Results will also be published on the study website (www.medscinet.net/ukpcn/above), and through university, clinical and PPI networks using email and social media.

18. REFERENCES

1. Mangham LJ, Petrou S, Doyle LW, Draper ES, Marlow N. The cost of preterm birth throughout childhood in England and Wales. *Pediatrics* 2009; **123**(2): e312-27.

2. Watson HA, Carter J, David AL, Seed PT, Shennan AH. Full dilation cesarean section: a risk factor for recurrent second-trimester loss and preterm birth. *Acta Obstet Gynecol Scand* 2017.

3. Hickland Maria SL, Carter Jenny, Watson Helena, Cauldwell Matthew, Shennan Andrew. Efficacy of abdominal versus vaginally placed cervical cerclage in women with a previous second-stage C-section. Accepted as an oral presentation. Preterm Birth Conference Bristol September 2018; 2018.

4. Suff N, Xu VX, Glazewska-Hallin A, Carter J, Brennecke S, Shennan A. Previous term emergency caesarean section is a risk factor for recurrent spontaneous preterm birth; a retrospective cohort study. *Eur J Obstet Gynecol Reprod Biol* 2022; **271**: 108-11.

5. Watson HA, Carter J, David AL, Seed PT, Shennan AH. Full dilation cesarean section: a risk factor for recurrent second-trimester loss and preterm birth. *Acta Obstet Gynecol Scand* 2017; **96**(9): 1100-5.

6. Alfirevic Z, Owen J, Carreras Moratonas E, Sharp AN, Szychowski JM, Goya M. Vaginal progesterone, cerclage or cervical pessary for preventing preterm birth in asymptomatic singleton pregnant women with a history of preterm birth and a sonographic short cervix. *Ultrasound Obstet Gynecol* 2013; **41**(2): 146-51.

7. Shennan AH, Story L, Royal College of Obstetricians G. Cervical Cerclage: Green-top Guideline No. 75. *BJOG* 2022; **129**(7): 1178-210.

8. Shennan A, Chandiramani M, Bennett P, et al. MAVRIC: a multicenter randomized controlled trial of transabdominal vs transvaginal cervical cerclage. *Am J Obstet Gynecol* 2020; **222**(3): 261 e1- e9.

9. Carter, J., Deery, J., Chandiramani, M. and Shennan, A., 2023. “I had given up on being a mother”: a survey of 183 women’s experience of transabdominal cerclage (TAC). BMC Pregnancy and Childbirth, 23(1), pp.1-8.

19.APPENDICES

19.1. Information with regards to Safety Reporting in Non-CTIMP Research

	Who	When	How	To Whom
SAE	Chief Investigator	-Report to Sponsor within 24 hours of learning of the event -Report to the MREC within 15 days of learning of the event	SAE Report form for Non-CTIMPs, available from NRES website.	Sponsor and MREC
Urgent Safety Measures	Chief Investigator	Contact the Sponsor and MREC Immediately Within 3 days	By phone Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action.	Main REC and Sponsor Main REC with a copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt.
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion)	Annual Progress Report Form (non-CTIMPs) available from the NRES website	Main REC
Declaration of the conclusion or early termination of the study	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination)	End of Study Declaration form available from the NRES website	Main REC with a copy to be sent to the sponsor

		The end of study should be defined in the protocol		
Summary of final Report	Chief Investigator	Within one year of conclusion of the Research	No Standard Format However, the following Information should be included:- Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to participants	Main REC with a copy to be sent to the sponsor

19.2. "Implementation and operation of MedSciNet's database applications for Medical Studies and Registers."

MedSciNet AB

MedSciNet™
Internet Database Solutions

Implementation and operation of MedSciNet's database applications for Medical Studies and Registers.

1. Overview

MedSciNet delivers customer-specified database applications for Medical Studies and Registers accessible for the users over the Internet. Functionally this means that MedSciNet on their Internet Server creates a homepage containing advanced functions for the customer. The service is then provided continuously to the customer's users.

The homepage consists of two parts: An open part and a part protected by username and password.

The open part of the home page is used for publication of information, news etc. It is developed according to the customer's requirements.

The protected part of the homepage contains the customer application. The application includes interfaces to the database (the database management system is Microsoft SQL Server) and to Internet for data entry, a reporting module, a descriptive statistics module with graphic presentation, an export module, an alert module, and an administrative module.

The system allows for flexible validation rules for the entered data.

If necessary the application can be connected to external data sources, e.g. computerized journaling systems and population databases.

The application is protected by a username / password login with 128 bits encryption. License for a Secure Server ID is included. (More information is available on www.verisign.com .)

The application includes an automated user and an event logging system.

Medscinet deploys a validated systems that complies with Good Clinical Practice (GCP) predicate rule requirements, laws, and regulations for clinical trial conduct and FDA 21 CFR 11 for electronic record and signature use. The applications are also compatible with the rules of HIPPA, NIH and HL7 as well as the European (CENTC-251) recommendations and requirements. More information is available on
http://www.fda.gov/ora/compliance_ref/part11/ .
http://www.hl7.org/
http://www.centc251.org/

Medscinet applications export data to SAS and other Statistical Software, comma separated value (CSV), or Microsoft Excel format and integrates with third–party reporting solutions like Cognos, Business Objects and many others.
The applications may streamline report submission to global regulatory agencies, creating, sending, receiving, and importing E2B files in XML and many other formats

The application can handle a large number of simultaneous users (> 1 000) and if necessary additional server capacity can be added to accommodate a virtually unlimited number of users. There is no limit of the number of participating hospitals / units etc. and the size of the database is adjusted to the need.

MedSciNet Applications 1 January 2008

2. Building the application

MedSciNet creates an application and database with necessary functionality accessible over the Internet.

The work is planned together with the customer based on the customer's specific requirements and includes the following:

1. Analysis
2. Database modeling
3. Programming of the application
4. Implementation
5. Complete test of the application

The different activities are described in more detail below:

Analysis

In the Analysis phase the whole implementation process is planned. The customer's requirements are defined and a project Plan is written. The Analysis phase addresses database, user interface, users, requirement for output data, system load, security etc. and results in the detailed Project Plan.

Database modeling

Before the database itself is created, a discussion with the customer takes place in order to define the optimal database structure, not only in terms of technical and operational matters but also including the customer's information needs. In this phase MedSciNet's long experience of medical studies and registers is very valuable in order to simplify and optimize the structure of the database as well as the users' handling of the application.

Programming of the application

In the programming phase, MedSciNet creates the application according to the detailed Project Plan and the database model. A large number of standardized modules are used to make the implementation more efficient and to make the application more robust and operational secure.

Implementation

When the application has been developed, MedSciNet transfers the application to their Production Server and connects it to the security system, user administration system etc. Finally the application is documented.

Complete test of the application

When the application has been created and installed on the Production Server an extensive test of the whole application is performed to verify that all the agreed functions have been implemented according to the agreements. The application is then handed over to the customer for operational production.

3. Application delivery (Operation and maintenance)

When the application has been put in production MedSciNet delivers the functionality to the customer's users (who may be spread all over the world) from their production Server over the Internet. The users need only a modern PC including a web browser and an Internet connection at a reasonable speed.

The application delivery includes:

1. Continuous connection to the Internet
2. Capacity, functionality, and maintenance of the server functions
3. Database management
4. Daily back-up with weekly back-up media stored in fireproof location
5. Customer support including minor modifications within the existing database

The different functions are described in detail below:

3.1. Continuous connection to the Internet

MedSciNet's Production Server is connected to the Internet via a link with sufficient speed so that the customers can access their applications with high availability and capacity and with acceptable response times.

3.2. Capacity, functionality, and maintenance of the server functions

MedSciNet delivers the customer's application via the Internet from their Production Server. The customer can access advanced server functions and a high server capacity without investing in his own server equipment. The equipment is maintained and updated continuously by MedSciNet in order to provide high availability and security.

3.3. Database management

Complex databases require maintenance to optimize performance etc. This function is included in the application operation.

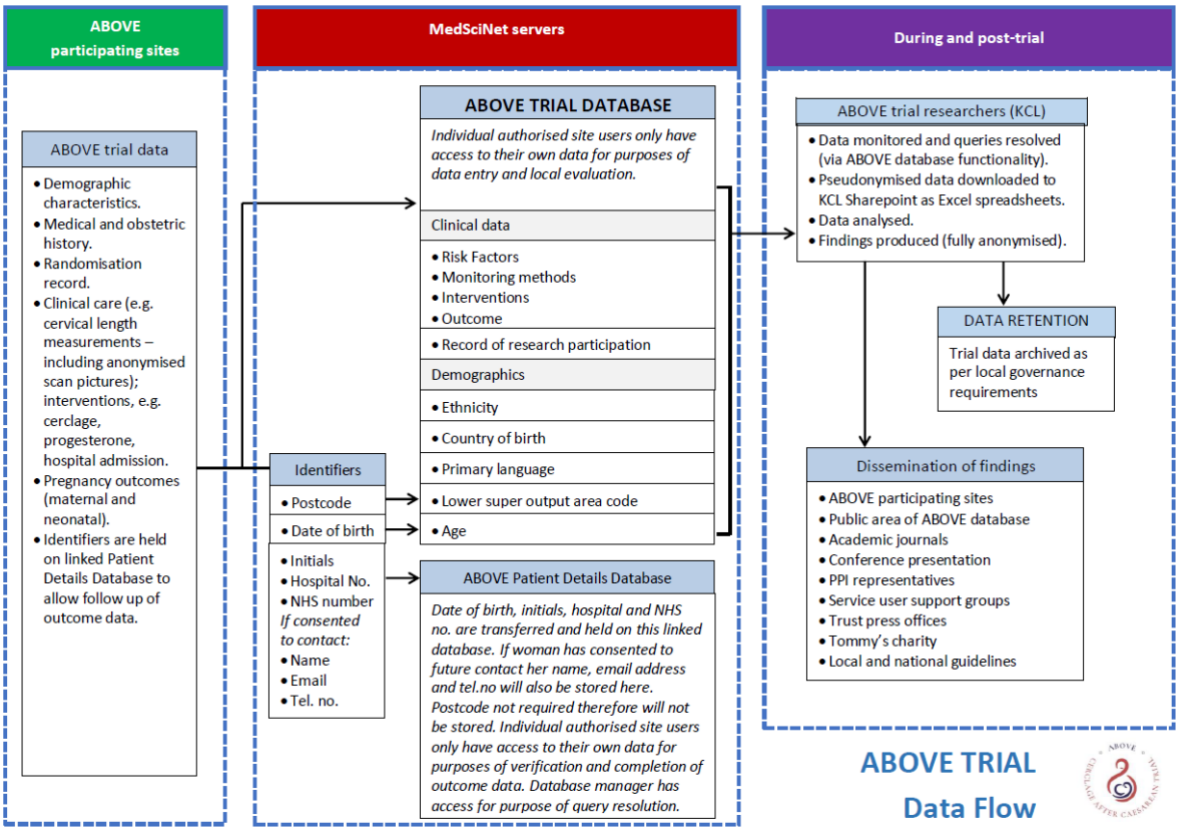
3.4. Daily back-up with weekly back-up media stored in fireproof location

Back-ups are taken of both the database and the application in itself, resulting in high security and protection from fire, damage or human mistakes.

3.5. Customer support including minor modifications within the existing database

MedSciNet's commitments include retaining documentation of the application, error correction, advice in operational matters etc. Since several applications run in operation for several years, minor modifications and added features are required. MedSciNet is committed to implement such changes, and minor modifications within the existing database may be made free of charge.

19.3. ABOVE trial data flow chart



19.4. ABOVE GANTT chart