St George's University Hospitals NHS Foundation Trust

Study Protocol Template (non CTIMP Interventional)

Study Title: Emergency Cerclage in Twin Pregnancies at Imminent Risk of Preterm Birth: an Open-Label Randomised Controlled Trial

ENCIRCLE Trial (Emergency Cerclage in Twin Pregnancies at Imminent Risk of Preterm Birth: an Open-Label Randomised Controlled Trial)

Sponsor's Project Number: 17.004
REC Reference Number: 17/EE/0040
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Statement

The Chief Investigator (CI) and the Sponsor representative have discussed this protocol version. The investigators agree to perform the investigations and to abide by this protocol except where departures from it are mutually agreed in writing.

The Investigator agrees to conduct the trial in compliance with the protocol, GCP, the Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005 2nd Edition), the Sponsor's SOPs, and other regulatory requirements as appropriate.

This protocol has been written in accordance to the Sponsor's procedure identified as: JREOSOP0039 "Protocol Design" and is intended for use at UK sites only

Chief Investigator Asma Khalil Consultant in Obstetrics and Fetal Medicine St George's University Hospitals NHS Foundation Trust	Signature 	Date 20.11.2016

Acknowledgements and Protocol contributories

Contents

1 List of abbreviations

CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
ICF	Informed Consent Form
ISF	Investigator Site File
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIS	Participant Information Sheet
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee

2 Roles and Responsibilities

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3 Study synopsis

Brief title:	ENCIRCLE trial
Official title:	Emergency Cerclage in Twin Pregnancies at Imminent Risk of Preterm Birth: an Open-Label Randomised Controlled Trial
Sponsor reference number:	17.0004
Public database identifier	TBC
Study design	Pilot randomised controlled trial
Study Population/disease condition	**<u>2 groups</u>** • Twin pregnancies between 14 – 26 weeks' gestation presenting with an open cervix • Monochorionic twin pregnancies complicated by twin-to-twin transfusion syndrome (TTTS) treated by Laser surgery between 16+0 and 26+0 weeks' gestation in whom a short cervix (<15mm) is identified
Eligibility criteria:	***Inclusion criteria:*** • Twin pregnancies presenting with an open cervix between 14 and 26 weeks of gestation, OR • Twin pregnancies complicated by TTTS treated by Laser surgery between 16+0 and 26+0 weeks' gestation in whom a short cervix (<15mm) is identified. • Age >18 years • Informed consent
	Exclusion criteria: • Cervical dilatation ≥5cm • Amniotic membranes prolapsed beyond external os into the vagina, unable to visualise cervical tissue • Preterm premature rupture of the membranes (PPROM) at the time of diagnosis of dilated cervix • Major fetal malformations unrelated to TTTS • Intrauterine death of one or both fetuses • Symptoms or signs of threatened imminent delivery, e.g. painful regular uterine contractions, active vaginal bleeding, history of ruptured membranes • Suspected chorioamnionitis [based on maternal uterine tenderness, a temperature of 38°C or greater, significant leucocytosis (>15,000 x 10^6/L) or elevated C-reactive protein (>15 mg/L), or maternal tachycardia].

	• Placenta praevia • Monochorionic monoamniotic twin pregnancies • Prophylactic cervical cerclage • Women who are not able to give valid consent, e.g. unconscious or severely ill • Mental health disorder which impairs the ability to give fully informed consent • Women under the age of 18 years • Higher order multiple pregnancies
Target number of participants	We have more than 8 UK centres willing to participate in the study. One concern is that recruitment to this study might be difficult, as women might not agree to be randomised to no intervention. As this a pilot study, we plan to recruit 20 women in the first group (13 women in the cerclage group and 7 women in the control group) and 11 women in the second group (7 women in the cerclage group and 4 women in the control group), so 31 participants in total. The rational for choosing randomisation of 2:1 (cerclage:expectant management) is that women often request the cerclage as a treatment in view of the favourable published observational data and the extremely poor outcome in the pregnancies which are expectantly managed. Therefore, participating in the trial has 2 out of 3 chance of receiving the cerclage and 1 out of 3 of being randomised to the expectant management. This pilot trial will provide the data required for a full funding application to the NIHR RFPB programme.
Criteria for evaluation	**Primary outcome measure(s)** Time to delivery (from randomisation to birth).
	Secondary outcome measure(s) 1. Gestation at delivery 2. Preterm birth before 28, 32 and 34 weeks' gestation 3. Birthweight 4. Stillbirth 5. Neonatal death 6. Survival to discharge 7. Days of admission to the neonatal intensive care unit 8. Composite outcome of stillbirth, neonatal death, intraventricular haemorrhage, periventricular leukomalacia, respiratory distress syndrome, bronchopulmonary dysplasia, retinopathy of prematurity, necrotising entercolitis, proven neonatal sepsis, or the need for ventilation 9. Days of maternal admission for preterm labour

	10. Maternal morbidity (defined as thromboembolic complications, chorioamnionitis, urinary tract infection treated with antibiotics, pneumonia, endometritis, eclampsia, HELLP syndrome, death, or any other significant morbidity)
Sources of funding	This study is planned to take place in a number of centres in the UK. The trial is partially funded by the Twins And Mutiple Births Association (TAMBA).
Anticipated start date:	March 1st, 2017
Anticipated primary completion date:	December 31st, 2018
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4 Background

Preterm birth remains the leading cause of perinatal mortality and morbidity.[1] It is also associated with societal and economic burden, with a substantial risk of long-term mental and physical disability.[1] Twin pregnancies are at increased risk of perinatal mortality and morbidity largely due to preterm birth and complications related to monochorionicity such as twin to twin transfusion syndrome (TTTS).[2-5] Up to 2-3% of births in the UK are from multiple pregnancies and the incidence continues to rise, mainly due to increasing maternal age and the widespread use of assisted reproductive technologies.[2] More than half of twin pregnancies deliver before 37 weeks and approximately 15% have preterm birth prior to 34 weeks' gestation.[2,6] Adverse neonatal outcomes include neonatal death, respiratory and neurological complications, the likelihood of which are related to the gestational age at delivery, ranging from 77% in those born before 28 weeks to less than 2% at term.[7]

Cervical insufficiency, defined as painless second-trimester cervical dilatation, is a well-recognised aetiology of preterm birth. In twin pregnancies measurement of cervical length can be used to predict those at increased risk of spontaneous early preterm delivery.[2,8-10] However, an effective prevention strategy for preterm delivery has yet to be discovered. In singleton pregnancies, progesterone treatment in women identified as being at increased risk of preterm birth was associated with an almost 50% reduction in the incidence of preterm birth before 34 weeks.[11-13] Furthermore, in women at increased risk of (singleton) preterm labour, placement of cervical cerclage when cervical shortening was detected has been associated with a reduction in the risk of preterm birth.[14,15] Unfortunately, however, preventive measures such as bed rest, progesterone therapy and cervical cerclage, have had disappointing results in twin pregnancies.[11,16-19] In fact, bed rest was associated with a significant *increase* in the rate of early preterm delivery. Progesterone therapy and elective cervical cerclage did not reduce the risk significantly.[11,17-20]

In women presenting with an already dilated cervix and/or bulging membranes in the second trimester, the rate of preterm birth has been reported to be as high as 90%, leading to miscarriage, neonatal death or extreme prematurity, and often associated with chorioamnionitis.[21-25] According to the published observational and limited randomised controlled trials, placement of an emergency cerclage was associated with a longer mean cerclage-to-delivery interval, and lower rates of preterm delivery before 34 weeks and of neonatal morbidity.[21-26] Therefore, emergency cerclage is likely to be associated with improved perinatal outcome in a cohort of pregnancies with a painless dilated cervix putting them at very high risk of extremely preterm birth. [21-26] However, most of these studies included singleton pregnancies. In their trial including 11 twin pregnancies, Gupta et al reported that emergency cerclage was associated with a "good outcome", where the pregnancy reached 32 weeks, with a healthy neonate in 36.4% of twin pregnancies.[27] In these studies, predictors of poor outcome included prolapsed membranes, evidence of intra-amniotic or systemic infection, symptomatic presentation, cervical dilatation greater than 3 cm, or gestational age beyond 22 weeks at placement of the cerclage.[27,28]

There are no randomised clinical trials investigating the role of emergency cerclage solely in multiple pregnancies. Only one randomised study included a very small number of twin pregnancies, along with several singleton pregnancies.[21] This compared a group of 13 women (10 singleton and 3 twin pregnancies) allocated to emergency cerclage with a second group of 10 women (6 singleton and 4 twin pregnancies) who had bed

rest only. This study demonstrated that the cerclage group did significantly better compared with the bed-rest 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 compound neonatal morbidity, 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). The main criticism of this study was its very small size. Observational studies in twin pregnancies have reported promising results.[29,30] Levin et al reported the pregnancy outcome in 14 women with twin gestations complicated by cervical shortening/effacement only or bulging membranes through the external os, who underwent emergency cerclage. The average time interval between cerclage placement and delivery was 80.2 days in the group with cervical shortening/effacement, and 48.5 days in the group with bulging membranes.[29] More recently, Aguilera et al reported mean pregnancy prolongation of 60.25 days with 76.9% neonatal survival in a case series of 12 multiple pregnancies with painless cervical dilation and exposed fetal membranes that underwent emergency cerclage. A recent retrospective cohort study has demonstrated that the combination of cerclage, indomethacin, and antibiotics in twin pregnancies with cervix dilated ≥1 cm before 24 weeks was associated with significantly longer latency period from diagnosis to delivery (6.7 weeks; 10.5 vs 3.7 weeks), decreased incidence of spontaneous preterm birth at any given gestational age (52.6% vs 94.7%, 44.7% vs 89.4%, 31.6% vs 89.4% for preterm birth <34 weeks, <32 weeks and <28 weeks' gestation, respectively), and improved perinatal outcome (reduced perinatal mortality 27.6% vs 59.2%, neonatal intensive care unit admission 75.9% vs 97.6%, and composite adverse neonatal outcome 33.9% vs 90.5%) when compared with expectant management.[31] A summary of the studies of cerclage in twin pregnancies with dilated cervix is shown in Table 1.

These results are promising, but these studies are retrospective, include small numbers of pregnancies and are likely to be biased in view of their observational nature and the possibility of selecting less favourable cases for intervention versus conservative management. Moreover, there are risks associated with insertion of an emergency cerclage, such as rupture of the membranes during the procedure, which inevitably is followed by delivery.

Severe TTTS, which affects 10-15% of monochorionic twin pregnancies, is associated with an over 50% risk of delivering before 34 weeks.[32,33] Studies have demonstrated that, in addition to factors predicting fetal survival, such as fetal Doppler or Quintero staging, cervical length is a strong predictor of preterm delivery in pregnancies complicated by TTTS.[33,34] Cervical shortening in TTTS is likely to be mainly because of increased pressure in the amniotic cavity secondary to the severe polyhydramnios.[35,36] Therefore, it could be argued that in this subgroup of twin pregnancies, emergency cerclage following laser therapy might be an effective intervention in those pregnancies with a short cervix. In fact, an observational study has reported that placement of an emergency cerclage in these pregnancies was associated with prolongation of the pregnancy.[34] In this small study which included 5 pregnancies with a short cervix (<15mm; less than the 5th centile) which were managed expectantly and 9 pregnancies with a short cervix which had emergency cerclage inserted following the Laser surgery, the gestational age at delivery was 23.1 weeks and 30.5 weeks, respectively (p=0.004).[34] Furthermore, there were 16 (89%) and 4 (40%) surviving twins in cases

with and without cerclage, respectively (p=0.01).[34] Despite these promising results, a multicentere, retrospective cohort study including 163 patients with a short cervix (defined as ≤25mm) at the time of the Laser surgery for TTTS, reported no difference in the gestational age at delivery (28.8 ± 5.4 vs 29.1 ± 5.6 weeks with and without cerclage, respectively) or perinatal mortality between the group which had cerclage (n=79) and the group which did not (n=84).[37] However, the cerclage was performed more frequently for a cervical length of ≤ 15 mm, so this group was at a higher risk of preterm birth and adverse outcome. To date there are no randomised trials investigating the role of emergency cerclage in these high-risk pregnancies.

The study hypothesis is that the placement of an emergency cervical cerclage prolongs the pregnancy in (1) twin pregnancies with a dilated internal cervical os between 14+0 and 26+0 weeks, and (2) in monochorionic twin pregnancies complicated by TTTS treated by Laser surgery between 16+0 and 26+0 weeks' gestation in whom a short cervix (<15mm) is identified.

5 Study objectives

5.1 Primary objective

The main objective of the study is to investigate whether the insertion of an emergency cerclage will prolong the pregnancy in twin pregnancies in each of the two study groups.

5.2 Secondary objectives

Other study objectives include determining the effect of the emergency cerclage on adverse perinatal outcome, defined as preterm birth less than 32 weeks' gestation, a composite outcome of stillbirth, neonatal death, intraventricular haemorrhage, periventricular leukomalacia, respiratory distress syndrome, bronchopulmonary dysplasia, retinopathy of prematurity, necrotising entercolitis, proven neonatal sepsis, or the need for ventilation. We also plan to investigate the length of admission to the neonatal unit and maternal morbidity.

6 Trial design

Open-label multi-centre randomised controlled trial.

7 Participation selection criteria

There will be no exceptions (waivers) to eligibility criteria prior to participant inclusion into the study. Any questions raised about eligibility should be addressed prior to entering the participant.

The eligibility criteria have been carefully considered and are standards used to ensure the trial results can be appropriately used to make future treatment decisions for other people

with similar disease or medical condition. It is therefore vital that exceptions are not made to the following detailed selection criteria.

All participants that are screened for inclusion into the study must be entered onto the Sponsor screening log JREOLOG0001 and will be assigned a sequential number. Participants will be considered eligible for enrolment into this trial if they fulfil all of the inclusion criteria and none of the exclusion criteria as defined below.

Eligible participants will be entered onto the Sponsors Subject ID log JREOLOG0002 and assigned a Trial specific Identification number in a pre-agreed format in accordance with Site Identifier and next sequential numerical value, e.g. SG001.

7.1 Inclusion criteria

- Twin pregnancies presenting with an open cervix between 14 and 26 weeks, OR
- Monochorionic twin pregnancies complicated by TTTS treated by Laser surgery between 16+0 and 26+0 weeks' gestation in whom a short cervix (<15mm) is identified.

- Age >18 years
- Informed consent

7.2 Exclusion criteria

- Cervical dilatation ≥5cm
- Amniotic membranes prolapsed beyond external os into the vagina, unable to visualise cervical tissue
- Preterm premature rupture of the membranes (PPROM) at the time of diagnosis of dilated cervix
- Major fetal malformations unrelated to TTTS
- Intrauterine death of one or both fetuses
- Symptoms or signs of threatened imminent delivery, e.g. painful regular uterine contractions, active vaginal bleeding, history of ruptured membranes, or suspected chorioamnionitis [based on maternal uterine tenderness, a temperature of 38°C or greater, significant leucocytosis (>15,000 x 10^6/L) or elevated C-reactive protein (>15 mg/L), or maternal tachycardia].[38]
- Placenta praevia
- Monochorionic monoamniotic twin pregnancies
- Prophylactic cervical cerclage
- Women who are not able to give valid consent, e.g. unconscious or severely ill
- Mental health disorder which impairs the ability to give fully informed consent
- Women under the age of 18 years
- Higher order multiple pregnancies

8 Participant Recruitment process

Patient recruitment at a site will commence only once there is evidence that the following approval/essential documents are in place:

1. REC approval

2. Final sponsorship and host site permissions

All subjects who wish to enter the study will be fully screened and consented by the Chief Investigator or an appropriate delegate.

Patients will be invited to participate in the trial if they have (1) a twin pregnancy and present with an open cervix or (2) a monochorionic twin pregnancy complicated by TTTS treated by Laser surgery, and have a short cervix. These women usually present with an incidental finding of a shortened dilated cervix on cervical length surveillance, or they present with subjective complaints of increased pelvic pressure or vaginal discharge and then undergo cervical length assessment (either ultrasound or speculum examination, or both). Eligible women will be identified by staff in the antenatal clinic, delivery suite, ultrasound department, fetal medicine unit and day assessment unit. All eligible women will be given verbal and written information about the trial and be invited to take part.

The trial will be conducted by the sponsor, participating sites and all investigators in accordance with the protocol, the Declaration of Helsinki, the guidelines on Good Clinical Practice (GCP) and all legal requirements, including applicable national legislation, for the conduct of this trial.

9 Study procedures

9.1 Informed consent

It is essential that all trial teams undertaking the informed consent process have signed the Sponsor's Delegation of Responsibilities Log JREOLOG0004 to ensure that the person has been delegated the responsibility by the study CI/PI. All personnel taking informed consent must be GCP trained. Refer to Sponsor SOP JREOSOP0027.

Informed consent will be obtained from eligible women by a member of the research team after confirming the eligibility, inclusion and exclusion criteria.

The Principal Investigator or designee will explain to the patient that she is under no obligation to enter the trial and can withdraw at any time during the trial, without having to give a reason. Those who agree to take part will be asked to sign a Consent Form prior to any study investigation or treatment. The participants' general practitioners will be informed in writing about the trial, and the hospital notes of those receiving an emergency cerclage will be marked with a sticker labelled 'emergency cerclage'. **Those who decline to participate in the randomised trial will be asked if they consent to the research team following up their pregnancy outcomes and recording anonymised pregnancy and neonatal outcome data in the study registry. The consent form will allow women to**

specify that they are willing for their data to be collected but prefer not to participate in the randomised controlled study.

A copy of the signed Informed Consent Form (ICF) along with a copy of the most recent approved Patient Information Sheet (PIS) will be given to the study participant. An original signed & dated ICF will be retained in the medical notes and a copy will be placed in the Investigator Site File (ISF). A copy of the signed ICF will also be given to the participant.

If new information results in significant changes to the risk-benefit assessment, the ICF will be reviewed and updated as necessary. All participants, including those already being treated, will be informed of the new information, given a copy of the revised ICF and asked to re-consent if they choose to continue in the study.

9.2 Randomisation procedure

Within each of the two study groups, participants will be randomly assigned (2:1) to the 'emergency cerclage' or 'control/expectant management' groups, using a web-based application. Participants and investigators will be aware of the allocation, as masking will be impossible because of the nature of the intervention. At the time of randomisation, the patients will be informed of the possible side-effects of emergency cerclage, such as risk of rupture of the membranes during the procedure.

9.3 Discontinuation/withdrawal of participants and stopping rules

In consenting to the trial, participants are consenting to trial treatments, trial follow-up and data collection. However, an individual participant may stop treatment early or be stopped early for any one of the following reasons:

Intercurrent illness that prevents further protocol treatment

Any change in participant's condition that in the investigator's opinion justifies the discontinuation of treatment.

Withdrawal of consent by the participant

As participation in the trial is entirely voluntary, the participant may choose to discontinue participation at any time without penalty or loss of benefits to which she may be entitled. Although not obliged to give a reason for discontinuing her participation, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights. Participants who discontinue study participation for any of the above reasons should remain in the study for the purpose of follow-up and data analysis.

If a participant chooses to discontinue they should be continued to be followed up as closely as possible to the follow-up schedule defined in the protocol, providing they are willing. However, if the participant confirms they do not wish to participate in the scheduled follow-up data collection visits, then data that have already been collected should be kept and analysed according to the ITT principle for all participants who stop follow-up early.

Participants who stop the trial follow-up early will not be replaced.

9.4 Participant transfers

If a participant moves from the area making, continued follow-up at their consenting centre inappropriate, every effort should be made for them to be followed up at another sponsor approved trial centre. Written consent should be taken at the new centre and then a copy of the participant's CRF should be provided to the new centre. Responsibility for the participant remains with the original consenting centre until the new consent process is complete.

9.5 Lost to Follow-up

For studies conducted in the UK, the NHS number may be used to trace participants who may have changed their GP; specific consent may be required to utilise this.

9.6 Definition of the End of Trial

The trial will be completed as soon as 10 patients are included in each of the 4 arms. The End of the Trial is defined as the Last Patient Last Visit (LPLV) or the last data entry point. The REC and the Sponsor will be notified of the end of trial within 90 days of its planned completion or within 15 days if the study is terminated early.

10 Study Procedures

10.1 *Measurement of cervical length*

Cervical length will be measured in the usual way (part of the routine care; not considered as a specific study investigation). The woman will be asked to empty her bladder, placed in the lithotomy position, and the transvaginal probe will be placed in the anterior fornix of the vagina. A sagittal view of the cervix will be obtained and the calipers used to measure the distance between the triangular area of echodensity at the external os and the V-shaped notch at the internal os. Each examination will be performed over a period of around three minutes. In around 1% of cases, dynamic cervical changes, due to uterine contractions, are observed. In such cases the shortest measurement will be recorded. Presence or absence of funnelling/cervical dilatation at the internal os will be documented. The researchers will receive appropriate training on measurement of cervical length.

10.2 Screening for infections

Women will routinely (not considered as a specific study investigation) have bacteriological investigation. Treatment using the appropriate antibiotic will be given if there is an infection. If they are allocated to the cerclage group, the cerclage will be inserted after completion of the treatment.

An amniocentesis of the presenting twin might be performed, according to local protocols, to quantify amniotic glucose, leucocytes, IL-6 and leucocyte esterase levels and for microbiological film. If the initial assessment (within 24 hours) suggests the presence of infection [positive gram stain/amniotic fluid leucocyte count (≥6 leucocytes per high-power field or >30 cells/mm3) and/or amniotic fluid glucose concentration of ≤15 mg/dL][39], women will not be randomised.

10.3 Baseline assessments

The planned baseline assessments include assessment for the inclusion and exclusion criteria and data collection.

10.4 Interventions (Insertion of Cerclage)

A McDonald or Shirodkar-type rescue cerclage will be placed. The choice of surgical approach will be at the discretion of the operating clinician and in line with local common practice. The local practice will be clarified during the initial site capacity and capability assessments. The cerclage will be inserted by a competent obstetrician that has performed more than 15 cerclage procedures (including both elective and emergency). Distension of the urinary bladder and/or a Foley balloon will be used when necessary to replace the fetal membranes into the uterine cavity. Participants will be admitted pre-operatively and re-evaluated for the previously described exclusion criteria. They will receive peri-operative indomethacin for a period of between 6 and 24 hours. Post-operatively, women can be discharged if there is no uterine activity, rupture of the membranes, symptoms or signs of infection after 24 to 48 hours.

In women aiming for a vaginal birth, the cervical suture will be removed by a simple speculum examination at 35-36 weeks' gestation. If the woman is planning Caesarean section, the suture will be removed at the time of the Caesarean, at the end of the procedure.

However, if at any time rupture of the membranes occurs, or the mother develops symptoms or signs of uterine infection (chorioamnionitis), significant vaginal bleeding or regular painful uterine contractions, the cervical suture should be removed without delay.

If the pregnancy continues without complications, delivery will be planned in line with NICE guidelines (dichorionic twin pregnancy at 37 weeks' gestation and monochorionic twin pregnancy at 36 weeks' gestation).[2] Monochorionic twin pregnancy complicated by TTTS treated by Laser will have planned delivery at 34-36 weeks according to local protocols.

10.5 Follow-up visits

Follow-up visits for ultrasound assessment of fetal growth and cervical length will be carried out as per the local protocol (approximately every four weeks in dichorionic diamniotic twin pregnancies and every 2-3 weeks in monochorionic diamniotic twin pregnancies). A course of steroids (two intramuscular injections of betametasone/dexametasone 12 mg, 24 hours apart) will be administered in the week before any planned birth after 23 weeks' gestation.

10.6 Data collection

Information on the baseline characteristics of the patients, including demographic data, measurements for calculation of body mass index, and obstetrical and medical histories, will be collected at recruitment and recorded in a computer database. Data on pregnancy outcomes will be obtained from the hospital maternity and neonatal records or the patients' general medical practitioners. The obstetric records of all women who experience preterm birth will be examined to determine whether the delivery was medically indicated or

spontaneous. Spontaneous deliveries will include those with spontaneous onset of labour and those with rupture of membranes before labour. Quality control of the collected data and verification of adherence to protocols at the different centres will be performed on a regular basis by the trial coordinator.

10.7 Study flow chart and summary table of study assessments

Please refer to Appendix 1 and Appendix 2.

11 Study Timeline

Please refer to Appendix 3.

12 Safety Events

12.1 Definitions

Adverse Event (AE)—any untoward medical occurrence in a participant whether it is considered to be related to the intervention or not, that includes a clinical sign, symptom, or condition and/or an observation of a near incident. This does not include pre-existing conditions recorded as such at baseline; continuous persistent disease or a symptom present at baseline that worsens following administration of trial intervention.

Serious Adverse Event (SAE) - any Adverse Event or untoward medical occurrence in a trial participant that can be wholly or partly due to the intervention which resulted in any of the following:

- Death
- Is life-threatening (places the participant, in the view of the Investigator, at immediate risk of death)
- Requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay, even if it is a precautionary measure for observation, including hospitalisation for an elective procedure for a pre-existing condition)
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions)
- Consists of a congenital anomaly or birth defect (in offspring of participants regardless of time of diagnosis)
- Is another important medical condition

Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or require intervention to prevent one of the outcomes listed in the definition of serious AE will also be considered serious.

12.2 Recording Adverse Events (AEs)

All Adverse Events will be recorded in the hospital notes in the first instance.

A record of all AEs, whether related or unrelated to the treatment, will also be kept in the CRF and the Sponsor's AE Log JREOLOG0007.

If the Investigator suspects that the disease or condition has progressed faster due to the intervention, then she will report this as an unexpected adverse event to the sponsor.

12.3 Investigator Responsibilities relating to Safety Reporting

Collection, recording and reporting of AEs (including serious and non-serious events and reactions) to the Sponsor will be done according to the Sponsor's Safety reporting for non-CTIMP studies SOP JREOSOP0033.

All SAEs will be recorded in the hospital notes and the CRF, and the Sponsor's AE Recording Log JREOLOG0007. The AE Log will be sent to the Sponsor on request and every 2 months.

All SAEs will be reported both to the Sponsor via the JREO & REC using the SAE report form for research other than CTIMPs (non-CTIMPs) published on the HRA website.

The Chief or Principal Investigator, or a member of the research team, at any participating site will complete the SAE form which will be faxed both to the JREO on 020 8725 0794 or E-mailed to adverseevents@sgul.ac.uk, within 48hrs of the Investigator becoming aware of the event, and via email to the relevant REC.

The Chief or Principal Investigator will respond to any SAE queries raised by the Sponsor as soon as possible. Follow-up reports must continually be completed within an acceptable time-frame and sent as detailed above until the reportable event is considered resolved.

Events will be followed up until resolution; any appropriate follow-up information will be clearly marked as such and reported to the sponsor via the JREO as above in a timely manner.

Full reports should be completed and submitted to REC within 15 days of the event.

12.4 Notification of deaths

Only deaths that are assessed to be caused by the trial intervention will be reported to the Sponsor. This report will be immediate.

13 Data management and quality assurance

13.1 Confidentiality

All data will be handled in accordance with the Data Protection Act 1998.

The Case Report Forms (CRFs) will not bear the participant's name or other directly identifiable data. The participant's trial Identification Number (ID) only will be used for identification. The sponsor Subject ID log JREOLOG0002 can be used to cross reference participants' identifiable information.

13.2 Data collection tool

Case Report Forms will be designed by the CI. All data will be entered legibly in black ink with a ball-point pen. If the Investigator makes an error, it will be crossed through with a single line in such a way as to ensure that the original entry can still be read. The correct entry will then be clearly inserted. The amendment will be initialled and dated immediately by the person making the correction. Overwriting or use of correction fluid will not be permitted.

It is the Investigator's responsibility to ensure the accuracy of all data entered and recorded in the CRFs. The Staff Delegation of Responsibilities Log JREOLOG0004 will identify all trial personnel responsible for data collection, entry, handling and managing the database.

13.3 Incidental Findings

All subjects will be informed in a timely manner, both verbally and in writing, of any new information, findings or changes to the way the research will be conducted that are of potential relevance for participants or their families and might influence their willingness to continue in this study.

13.4 Data handling and analysis

The trial will use an online secure database. Quality Control will be applied at each stage of data handling to ensure that all data are reliable and have been processed correctly.

14 Archiving arrangements

The trial essential documents along with the trial database will be archived in accordance with the sponsor SOP JREOSOP0016. The agreed archiving period for this trial will be 10 years.

15 Statistical design

15.1 Endpoints

15.1.1 Primary endpoints

Time to delivery (from randomisation to birth).

15.1.2 Secondary endpoints

- Gestation at delivery
- Preterm birth before 28, 32 and 34 weeks' gestation
- Birthweight
- Stillbirth
- Neonatal death
- Survival to discharge

- Days of admission to the neonatal intensive care unit
- Composite outcome of stillbirth, neonatal death, intraventricular haemorrhage[40], periventricular leukomalacia, respiratory distress syndrome, bronchopulmonary dysplasia, retinopathy of prematurity[41], necrotising entercolitis[42], proven neonatal sepsis, or the need for ventilation
- Days of maternal admission for preterm labour
- Maternal morbidity (defined as thromboembolic complications, chorioamnionitis, urinary tract infection treated with antibiotics, pneumonia, endometritis, eclampsia, HELLP syndrome, death, or any other significant morbidity)

15.2 Sample size calculation

Study 1: Twin pregnancies presenting with an open cervix Group

We performed a sample size calculation based on the GA and preterm birth percentage (45% and 99% for with and without cerclage). Also included the outputs based on the preterm birth percentage of 45% and 95% for with and without cerclage.

An experiment with 6 women in the cerclage group and 3 women in the control group will have 80% power to detect the gestational age (at delivery) difference of 6 weeks or greater between cerclage and control groups at a significance level of 5%. Assuming the percentage of preterm birth at less than 32 weeks for the cerclage and control groups as 45% and 99%, respectively, an experiment with 15 women in the cerclage group and 8 women in the control group will achieve 80% power with the statistical significance of 5%. With the assumption that approximately 14 births occurring among these women in less than 32 weeks, an experiment with 20 women will also detect a hazard ratio of 0.34 or less in favour of the cerclage group - the cerclage group will be 66% less likely to give a birth at any time point before 32 weeks compared with the control group - with at least 80% power. These calculations do not include the loss to follow-up which should be considered by including one additional subject in each group.

Preterm birth percentage:

Cerclage group = 45%

Control group = 95%

Sample size:

Cerclage group = 19

Control group = 10

HR = 0.39

Study 2: Monochorionic Twin pregnancies complicated by TTTS treated by Laser surgery with short cervix (<15mm) Group

We have more than 8 UK centres willing to participate in the study. One concern is that recruitment to this study might be difficult, as women might not agree to be randomised

to no intervention. As this a pilot study, we plan to recruit 20 women in the Study 1 (13 women in the cerclage group and 7 women in the control group) and 11 women in the second Study 2 (7 women in the cerclage group and 4 women in the control group), so 31 participants in total. The rational for choosing randomisation of 2:1 (cerclage:expectant management) is that women often request the cerclage as a treatment in view of the favourable published observational data and the extremely poor outcome in the pregnancies which are expectantly managed. Therefore, participating in the trial has 2 out of 3 chance of receiving the cerclage and 1 out of 3 of being randomised to the expectant management.

An experiment with 13 women in the cerclage group and 7 women in the control group in the Study 1 will have 80% power to detect the gestational age (at delivery) difference of 6 weeks or greater between cerclage and control groups at a significance level of 5%. Similarly, an experiment with 7 women in the cerclage group and 4 women in the control group in the Study 2 will have 80% power to detect the gestational age (at delivery) difference of 6 weeks or greater between cerclage and control groups at a significance level of 5%. These calculations include the 5% loss to follow-up by including one additional subject in each group. The above calculations also assume that the between centre variability is negligible for the outcome of interest. This pilot trial will provide the data required for a full funding application to the NIHR RFPB programme.

15.3 Statistical analysis plan

Statistical analyses will be performed according to intention to treat. The primary analysis will compare the time to delivery (from randomisation to birth) in weeks. Other outcomes, such as gestational age at delivery, preterm birth before 28, 32 and 34 weeks' gestation, median birthweight, stillbirth, neonatal death and survival to discharge will be compared between the 2 arms of each study group as secondary outcomes. A number of statistical tests, including Pearson's chi-squared test [RR, (95%CIs)], Log-rank test [HR, (95%CIs)] and 2-sample student's t-test [mean ± SD], will be used to analyse the various outcomes.

16 Ethics and Research Governance requirements

Before any site can enrol patients into the trial, the Principal Investigator must ensure that written permission to proceed has been granted by that Trust Research & Development (R&D). The site must conduct the trial in compliance with the protocol as agreed by the Sponsor and which was accepted by the Research Ethics Committee (REC).

The Chief Investigator will be provided (via the Sponsor) with file indices, e.g. JREODOC0003 TMF index and JREODOC0004 ISF index, for use with SOP JREOSOP0019 'Preparation and Maintenance of the TMF'. The CI will be responsible for the maintenance of the TMF and may delegate the responsibility of ISF file maintenance to the PI at each participating site.

It is the responsibility of the PI at each site to ensure that all subsequent amendments gain the necessary approval. Refer to JREOSOP0011 'Management of Amendments'.

Within 90 days after the end of the trial, the CI and Sponsor will ensure that the REC is notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial. Refer to JREOSOP0015 'End of study declaration'.

The CI will supply an End of Study report of the clinical trial to the REC within one year after the end of the trial. The sponsor can provide JREODOC0059 End of study Report template.

16.1 Annual Progress Reports (APRs)

The Chief Investigator will prepare the APR in accordance with JREOSOP0043. Following review by the sponsor the report will be sent to the REC. The APR is due for submission annually within 30 days of the anniversary date on which the favourable opinion was given by the Ethics committee, until the trial is declared ended.

16.2 Notification of Serious Breaches of GCP and/or the protocol

Any Protocol Deviations or Violations will be documented using JREODOC0061, and entered onto the Sponsor's log JREOLOG0005. Potential Serious Breaches and Urgent Safety Measures will be recorded both on the Sponsor's Log JREOLOG0005 and processed according to JREOSOP0012 and where necessary JREOSOP0032.

A "serious breach" is a breach which is likely to affect to a significant degree:

(a) The safety or physical or mental integrity of the participants of the trial; or
(b) The scientific value of the trial.

The CI will notify the Sponsor immediately of any case where there is a possible serious breach.

16.3 Direct access to source data

The Investigator(s)/institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

17 Finance

The trial is partially funded by the Twins and Multiple Births Association (TAMBA), which is the largest UK charity providing support to multiple pregnancies. The funding will contribute to the salary of a research midwife who will coordinate the trial.

18 Insurance and indemnity

NHS bodies are liable for clinical negligence and other negligent harm to individuals covered by their duty of care. NHS Institutions employing researchers are liable for negligent harm caused by the design of studies they initiate.

19 Development policy

The sponsor, participating sites and all investigators involved in the study shall treat all information and data related to the study as confidential and with the proper respect for the privacy of each participant. The parties shall equally warrant to not disclose such information to third parties or disclose such publicly, but shall use such information solely for the purpose of this study. All data shall be coded or de-identified prior to transfer of such data to sponsor.

Parties have expressly agreed that any and all data collected and prepared in the context of the study shall be the property of the sponsor, provided that the participating sites shall remain the owner of their source data and may utilise such data as it deems appropriate without the approval of sponsor.

The participating sites and their proper investigators warrant that they shall not perform the study without having obtained the proper, written informed consent from each participant, in accordance with applicable legislation and as approved by the appropriate ethics committee/review board.

20 Publication policy

Publication: “Any activity that discloses, outside of the circle of trial investigators, any final or interim data or results of the Trial, or any details of the Trial methodology that have not been made public by the Sponsor including, for example, presentations at symposia, national or regional professional meetings, publications in journals, theses or dissertations.”

All scientific contributors to the Trial have a responsibility to ensure that results of scientific interest arising from Trial are appropriately published and disseminated. The Sponsor has a firm commitment to publish the results of the Trial in a transparent and unbiased manner without consideration to commercial objectives.

To maximise the impact and scientific validity of the Trial, data shall be consolidated over the duration of the trial, reviewed internally among all investigators and not be submitted for publication prematurely.

20.1 Before the official completion of the Trial

All publications during this period are subject to permission by the Sponsor. If an investigator wishes to publish a sub-set of data without permission of the Sponsor during this period, the steering committee shall have the final say.

20.2 Up to 180 days after the official completion of the Trial

During this period the Chief Investigator shall liaise with all investigators and strive to consolidate data and results, then submit a manuscript for peer review with a view to publication in a reputable academic journal or similar outlet as the Main Publication.

- The Chief Investigator shall be senior and corresponding author of the Main Publication.
- Insofar as is compatible with the policies of the publication outlet and good academic practice, the other Investigators shall be listed in alphabetic order.
- Providers of analytical or technical services shall be acknowledged, but will be listed as co-authors only if their services were provided in a non-routine manner as part of a scientific collaboration.
- Members of the Steering Group shall be acknowledged as co-authors only if they also contributed in other capacities.
- If there are disagreements about the substance, content, style, conclusions, or author list of the Main Publication, the Chief Investigator shall ask the Steering Group to arbitrate.

20.3 Beyond 180 days after the official completion of the Trial

After the Main Publication or after 180 days from Trial end date, any Investigator or group of investigators may prepare further publications. In order to ensure that the Sponsor will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to the Sponsor for review at least sixty (60) days prior to submission for publication, public dissemination, or review by a publication committee. Sponsor's reasonable comments shall be reflected. All publications related to the Trial shall credit the Chief and Co-Investigators as co-authors where this would be in accordance with normal academic practice and shall acknowledge the Sponsor and the Funders.

21 Statement of Compliance

The trial will be conducted in compliance with the protocol, Sponsor's Standard Operating Procedures (SOPs), GCP and the applicable regulatory requirement(s).

The study conduct shall comply with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws and statutes of the country in which the study site is located, including but not limited to the Human Rights Act 1998, the Data Protection Act 1998, the Human Medicines Regulations 2012, ICH GCP**,** the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (2008 Version), the NHS Research Governance Framework for Health and Social Care (Version 2, April 2005).

This study will be conducted in compliance with the protocol approved by the REC and according to GCP standards. No deviation from the protocol will be implemented without the prior review and approval of the Sponsor and REC except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the Sponsor and REC as soon as possible.

22 List of Protocol appendices

Appendix 1 Study flow chart

Appendix 2 Summary table of study assessments

Appendix 3 Timeline of the proposed pilot study

Appendix 4 Protocol Amendment/Revision History (chronological order) or a statement "There are currently no amendments"

23 References

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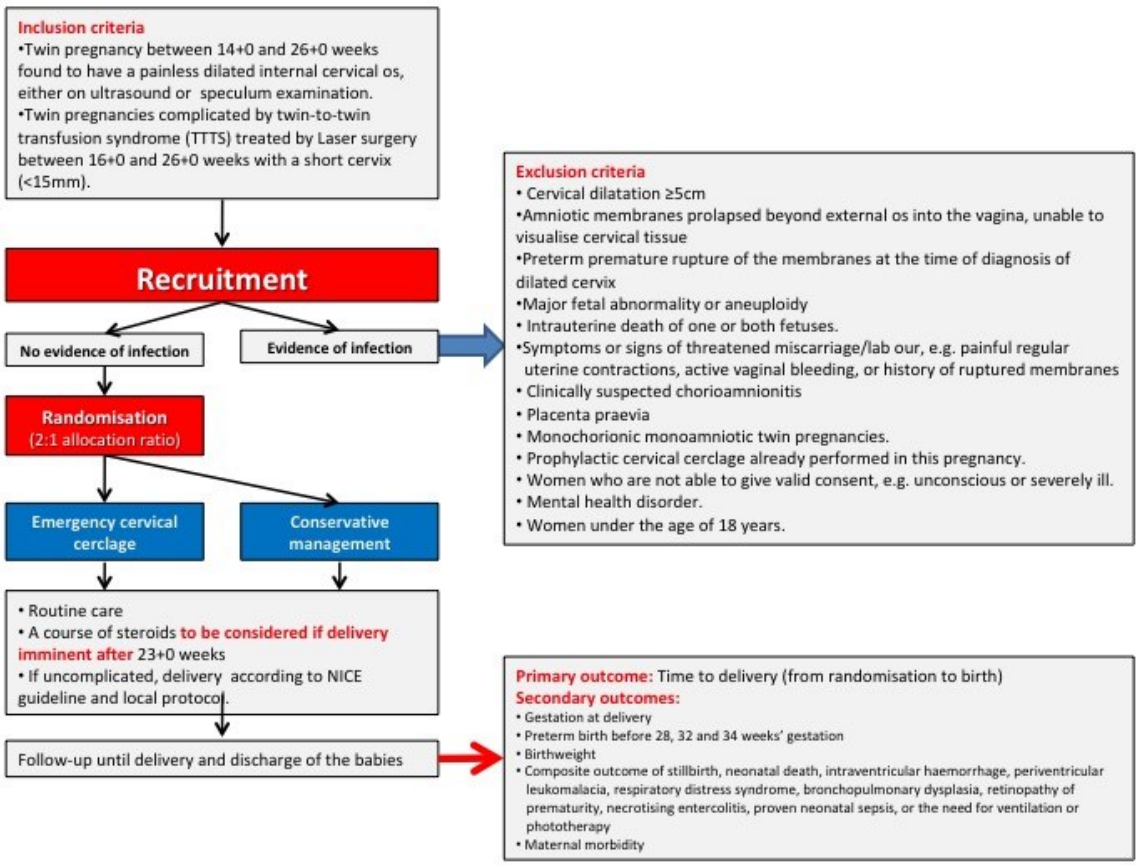
Table 1. Summary of studies on cerclage in twin pregnancy with dilated cervix.

First author and year	Study design	Cerclage	Controls (no cerclage)	GA	Amniocentesis	Antibiotics	Tocolysis	Time interval until delivery (days)	PTB <28 weeks	PTB <32 weeks	PTB <34 weeks	PPROM	Neonatal survival
Althuisius 2003	RCT	3	4	<27	No	No	No	No data	No data	No data	No data	No data	No data
Parilla 2003	RC	11	Not specified	21.4±2.2	No	N/A	N/A	No data	No data	No data	No data	No data	No data
Gupta 2010	RC	11	0	<27	No	Yes, not specified	Yes, not specified	No data	No data	No data	No data	No data	No data
Levin 2012	RC	14	0	20.1±2.5	No	All	No	71.1±44.6	2 (14.3%)	N/A	N/A	2 (14.3)	16/20 (80%)
Rebarber 2013	RC	12	0	14-23.8	12 (100%)	12 (100)	12 (100)	92 (26-145)	2 (16.6%)	3 (25%)	7 (58.3%)	2 (16.6%)	20/24 (83%)
Zanardini 20131	RC	14	0	16-26	No	14 (100)	14 (100)	69 (2-125)	3 (21%)	7 (50%)	7 (50%)	4 (29%)	24/28 (86%)
Miller 2014	RC	104	0	16-23.8	Not routinely used	56 (54.3)	69 (57.3)	69 (21-99)	35 (33.7%)	54 (51.9%)	N/A	35 (33.7%)	No data
Barnabeu 2015	RC	7	0	19.6±4.0	7 (100%)	7 (100)	7 (100)	12.1 (4-16)	2 (28%)	No data	3 (42.8%)	1 (14.2%)	14/14 (100%)
Roman 2016	RC	38	38	16-24	30 (79%)	36 (94%)	29 (76%)	73±39	12 (31.6%)	17 (44.7%)	20(52.6 %)	8 (21%)	50/76 (65.8)

RCT: randomised controlled trial; RC: retrospective cohort; GA: gestational age in weeks; PTB: preterm birth; PPROM: preterm pre-labour rupture of membranes.

Appendix 1

Study flow chart



Appendix 2. Summary table of study assessments.

Study Procedures	**Screening**	**Treatment**	**Follow-up (neonatal *discharge*)**
Informed consent	√		
Inclusion/exclusion criteria	√		
Data collection	√		
Demographics	√		
Baseline	√		
Screening	√		
Ultrasound	√		
Intervention		√	
Data collection/Telephone call			√

Appendix 3. Timeline of the proposed pilot study

Calendar year	**2017**										**2018**	
Calendar month	**March**	**April**	**May**	**June**	**July**	**August**	**Sept**	**Oct**	**Nov**	**Dec**	**Jan**	**Feb**
Ethics approval												
Database design												
Project set-up												
Co-ordination among the participating centres												
Recruitment												
Data collection												
Preliminary data analysis, literature review for a peer-reviewed paper												
Statistical analysis												
Writing and submission of a peer-reviewed paper and report to the funder												

Appendix 4

Protocol amendment /Revision History

Protocol Version and Date	New text