Protocol

Cerclage Suture Type for an Insufficient Cervix and its effect on Health outcomes Trial: a randomised controlled Trial of monofilament versus braided sutures for insufficient cervix

Short title: Cerclage Suture Type for an Insufficient Cervix and its effect on Health (C-STICH)

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Current Version Number: 1.1

Previous protocol versions and summary of changes

Version 1.0 to 1.1 – Correction of minor typos and clarification of inclusion and exclusion criteria.

ISRCTN 15373349

Funding Body:

National Institute for Health Research Health Technology Assessment Programme (NIHR HTA)

Grant reference number: **13/04/107**

Sponsor and Sponsor Roles

The University of Birmingham is the sponsor of C-STICH. Professor Khaled Ismail is the Chief Investigator.

The University of Birmingham is responsible for obtaining necessary approvals and for governance. The Trial Management Committee is jointly responsible for overseeing good clinical practice and the Investigators are responsible for obtaining informed consent and care of the participants.

Signatures

The investigators and the sponsor have discussed this protocol. The investigators agree to perform the investigation and to abide by this protocol except in case of medical emergency or where departures from it are mutually agreed in writing.

Chief investigator

University of Birmingham	Signature	Date

Sponsor

University of Birmingham	Signature	Date

Abbreviations

AE	Adverse event
AR	Adverse reaction
ASR	Annual Safety Report
BCTU	Birmingham Clinical Trials Unit at the University of Birmingham
CI	Chief Investigator
DMEC	Data Monitoring and Ethics Committee
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
ISRCTN	International Standard Randomised Controlled Trial Number
MREC	Multicentre Research Ethics Committee
PI	Principal Investigator – the local lead investigator for the XXX Trial
PIS	Participant Information Sheet
RR	Relative Risk
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee

Trial summary

Title

Cerclage Suture Type for an Insufficient Cervix and its effect on Health outcomes: a randomised controlled trial of monofilament versus braided sutures for insufficient cervix. (C-STICH)

Setting

Obstetric departments of UK hospitals

Trial Design

A multi-centre, open, randomised controlled trial of 900 women presenting at gynaecology units with insufficient cervix, scheduled to be treated by cervical cerclage.

Primary Objective

To examine the effect of using a monofilament suture material compared with a braided suture material on pregnancy loss rate (defined as miscarriage, stillbirth, neonatal death in the first week of life) and neonatal mortality up to one month post-delivery in women presenting with an insufficient cervix and treated with cervical cerclage.

Secondary objectives:

- To assess the effect of suture material on other pregnancy and neonatal outcomes
- To explore the variation in effect between McDonald's and Shirodkar's cerclage, especially with reference to bladder dissection
- To explore the variation in effect between the indication for cerclage
- To produce advice and a video clip to illustrate best practice in cerclage stitch insertion and removal

Target Population

Women over 18 years old with a singleton pregnancy presenting with indications for cervical cerclage.

Health Technologies Assessed

Monofilament or braided suture material

Lay Summary

Every year approximately 3750 women in the UK will have complications where their cervix (the neck of the womb) becomes loose and opens during the early months of pregnancy. This can require a stitch being sewn into the cervix in an attempt to keep it closed. This is often referred to as 'cervical suture' or 'cervical cerclage'. If this procedure is not performed the cervix can open too early and can result in a miscarriage or premature birth. Inserting a stitch into the cervix does not guarantee to keep the cervix closed, but it can sometimes allow the pregnancy to continue for a few more weeks.

The stitches used for this procedure are available in different sizes and materials. Some of the stitch threads are made from a single, smooth fibre (e.g. nylon) while others are composed of many fibres which are woven to form a fine braided or net-like structure. A survey of consultants in the UK has shown most use braided threads when they stitch the cervix merely because it is the traditional material used and because it is thought to offer strength and enhanced support to an otherwise loose cervix. However, this survey also revealed that some surgeons thought that bacteria could grow more easily in the spaces of the braided thread than on the surface of the monofilament line. This could increase the risk of infection which might cause an early labour. It is therefore essential to investigate whether thread-type used for stitching the cervix increases or decreases risk of infection.

The C-STICH study will therefore compare outcomes from the use of either smooth or braided stitches during this procedure. The results of this study can potentially save the lives of more than 300 babies a year in the UK alone who would otherwise be at risk of severe prematurity or miscarriage.

The best way to compare the two methods of treatment is to undertake a clinical trial where the nature of the stitch used is decided randomly. Computer software, specifically designed for this purpose will be used at a specialised unit at the University of Birmingham (Birmingham Clinical Trials Unit).

Eligible pregnant women can opt to be part of the STICH study if they are due a planned stitch in their cervix between 12 and 22 weeks into their pregnancy. Apart from the type of thread used, participants in the C-STICH study will receive identical medical treatment to those not taking part in the study. Several pregnancy outcomes will be collected though the central outcome for the study, as decided by the groups of women consulted, will be the risk of losing a baby during pregnancy or within a week of birth. Information will also be collected concerning the number of weeks pregnancy lasted prior to birth; whether the baby was admitted to a Neonatal Unit; the length of stay in the unit and any sign of vaginal or womb infection.

CONTENTS

1. BACKGROUND

1.1. Preterm birth

Pre-term birth (PTB) is one of the major challenges in obstetrics and neonatology globally. According to the office of national statistics, approximately 50,000 babies[1] are born prematurely each year. Approximately 1,500 of them die.

An early birth puts survivors at risk of serious long-term disabilities[2] and these outcomes pose a significant burden on parents as well as having economic implications on health services. It is estimated that 10% of healthcare resources in developed countries are spent on treating diseases in children resulting from PTB[3]. Cervical insufficiency (also called cervical incompetence) is one of the important causes of PTB for which cerclage has been one of the established management options[4,5,6].

1.1.1 The consequences of pre-term birth

The effects of PTB are often very severe and can be devastating for both the child and their parents. In the short term, preterm babies often require special care in the neonatal intensive care unit (NICU). In general, the earlier the preterm infant, the greater the likelihood that life support will be required, meaning a longer stay in the NICU.

Children born prematurely often have underdeveloped lungs meaning breathing problems are common in preterm infants and many will require ventilatory support. These babies may have breathing problems through the first year of life and an increased risk for developing asthma later.

The brain continues to develop after the time of birth. The more prematurely the baby is born the more likely it is to suffer an insult which will cause damage to the brain. This can result in the failure to attain developmental milestones or in physical disability.

In the longer term, babies born prematurely often have long-term difficulties such as:

- Behavioural and social-emotional problems
- Learning difficulties
- Increased risk of conditions such as Attention Deficit-Hyperactivity Disorder (ADHD)
- Increased risk for Sudden Infant Death Syndrome (SIDS)

These children are more likely to require early intervention and special education services. Upon reaching maturity, children born pre-term are more likely to suffer chronic diseases such as heart disease, hypertension and diabetes.

With over 50,000 babies being delivered prematurely each year in the UK, in addition to the often devastating effects on both the child and its parents, pre-term birth imposes a significant economic burden on the health care system.

1.2. Insufficient Cervix

The cervix is the narrow tube, usually about 2.5cm long that connects the uterus and vagina. Normally the lumen of the cervix remains slightly patent to allow the exit of menses and access of semen to the uterine cavity.

Following conception and implantation of the embryo, the cervix initially becomes more vascular and softens. The lumen becomes blocked with a mucus secretion from the endocervical glands, and the thick mucus plug acts as a protective barrier to ascending infections. During a normal pregnancy a dense mesh of collagen fibres ensures that the cervix remains firm, long and closed until late in the third trimester. At this point it usually starts to soften, efface and dilate as fluid is taken up by hydrophilic mucopolysaccharides in the interstices between the collagen bundles. As the supravaginal part of the cervix expands, the cervix shortens to prepare for labour and birth.

In some pregnant women the cervix effaces and dilates prematurely. These women may suffer a second trimester miscarriage or pre-term delivery as the uterus is unable to restrain the weight of the baby pressing on the dilated cervix.

1.2.1 Clinical presentation

There are no objective tests that can be done before pregnancy to reliably predict an insufficient or weak cervix. Historically, women were diagnosed clinically with cervical insufficiency after they had a history of second-trimester miscarriages or early preterm births preceded by spontaneous rupture of membranes or painless cervical dilatation with no other known cause.

More recently, regular transvaginal ultrasounds from 14 to 24 weeks of gestation can detect early cervical shortening and funnelling. As with many clinical presentations, cervical insufficiency cannot be viewed as a simple dichotomous diagnosis, but instead presents as a spectrum of risk, influenced by both the anatomy of the cervix and the processes leading to premature cervical effacement and dilatation.

At a later stage, a pelvic examination can be undertaken to see if the foetal membranes have prolapsed into the neck of the cervix.

1.2.2 Incidence

Approximately 3,750 pregnant women are diagnosed with an insufficient cervix in the UK each year[1].

1.2.3 Risk factors

Women considered to be more likely to experience an insufficient uterus during pregnancy are those who have had:

- Previous cervical cerclage
- A history of two or more mid-trimester losses or pre-term deliveries
- Previous cervical surgery / treatment including cervical loop biopsies

1.3. Current management of cervical insufficiency

Other than cerclage, very few treatments are available for cervical insufficiency and the evidence for their use is largely anecdotal.

1.3.1 Progesterone supplementation

The injection of the progesterone supplement hydroxyprogesterone caproate (Makena) during the second trimester has been suggested to help women who have cervical insufficiency, although the use of this pharmaceutical is contraindicated in women carrying multiple babies.

1.3.2 Cervical pessaries

Some clinicians promote the use of a device which sits inside the vagina and which helps reduce the pressure on the cervix. No reliable evidence is available to determine if the use of these devices is an effective treatment for cervical insufficiency.

1.3.3 Cervical Cerclage

Cervical cerclage is the placement of stitches in the cervix to hold it closed and has been described as "*a history-indicated suture performed as a prophylactic measure in asymptomatic women and normally inserted electively at 12–14 weeks of gestation*[8]". Perhaps its most common use is in the treatment for an insufficient cervix. During this procedure, which has been in use for over one hundred years, strong sutures are placed in the lumen of the cervix to hold it closed.

Alternatively, women considered at risk can be offered ultrasound surveillance of their cervix. Insertion of a cerclage can be undertaken as a therapeutic measure in cases of cervical length shortening seen on transvaginal ultrasound. Ultrasound-indicated cerclage is performed on asymptomatic women who do not have exposed fetal membranes in their vagina. Sonographic assessment of the cervix is usually performed between 14 and 24 weeks of gestation.

There are two types of cerclage performed vaginally: McDonald's[6] or Shirodkar's[4]. Depending on the technique used the suture may be removed shortly before the patient is ready to deliver.

- McDonald's cerclage is the most common, and is essentially a purse string stitch used to pinch the cervix shut; the cervix stitching involves placing a suture material at the upper part of the cervix while the lower part has already started to efface. This cerclage is usually placed between 12 weeks and 14 weeks of pregnancy. The stitch is generally removed around the 37th week of gestation.

- Shirodkar's cerclage is very similar, but the sutures pass through the walls of the cervix so they are not exposed. As Shirodkar's cerclage includes a bladder dissection it is technically more difficult than McDonald's method, but is thought (though not proven) to reduce the risk of infection. The Shirodkar procedure sometimes involves a permanent stitch around the cervix which will not be removed and therefore a Caesarean section will be necessary to deliver the baby.

1.4. The effectiveness for cervical cerclage

1.4.1 The evidence for cervical cerclage

Despite being in use for over one hundred years there is very little evidence drawn from high quality clinical trials. A recent Cochrane review concluded that cerclage reduces the incidence of early delivery but does not significantly reduce miscarriage rate or perinatal mortality.[9]

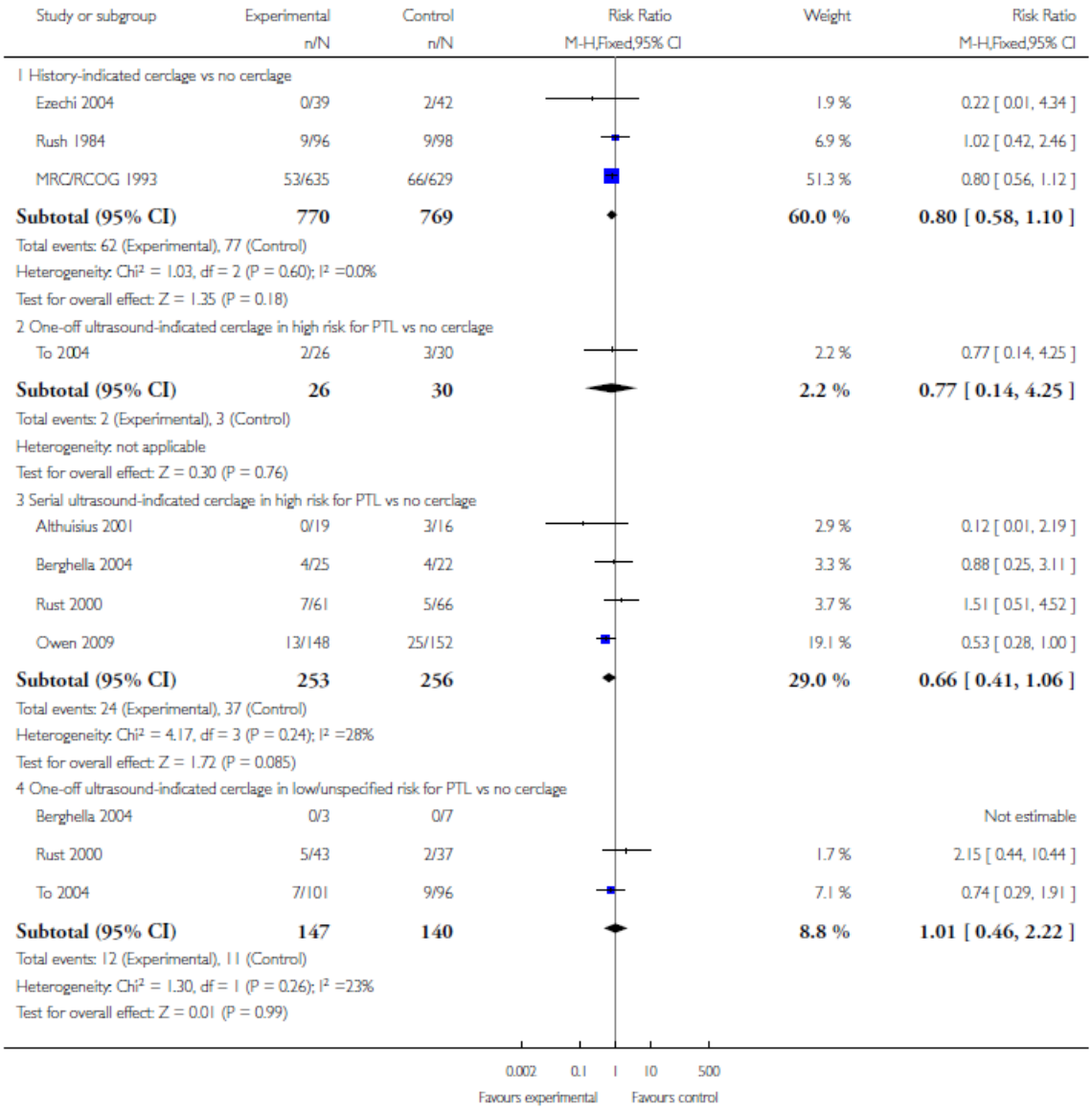
Figure 1 Results of the Cochrane review and meta-analysis of RCTs of cerclage for preventing pre-term birth.

Analysis 1.1. Comparison 1 Cerclage vs no cerclage, Outcome 1 All perinatal losses.

Review: Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy

Comparison: 1 Cerclage vs no cerclage

Outcome: 1 All perinatal losses



Traditionally, clinicians have used Mersilene® tape (a macroporous braided suture) for cervical cerclage because of its perceived strength and ease of removal. However, braided sutures, particularly mesh-like non-absorbable sutures, have been associated with an increased risk of

infection particularly when used in potentially contaminated surgical areas[10]. We hypothesise that as braided sutures would have been predominant in the studies reported the Cochrane report they may have unintentionally induced a bias in the conclusions and masked a true benefit of cerclage.

1.4.2 The influence of the suture material in gynaecological surgery

Using the categorisation criteria developed at the UCLA Lichtenstein Hernia Institute[11], mesh materials used in surgery are divided into four categories

Category	Type of mesh
I	Macroporous > 75 µM (Atrium® / Prolene®)
II	Microporous < 10 µM (Gore-Tex®)
III	Macroporous with braided filaments (PTFE / Mersilene®)
IV	Submicronic (Silastic®)

Table 1 Types of mesh

Clinically it has been reported that Type II and Type III meshes have a propensity to extrusion and infection, and there are a number of high profile products composed of Type II and Type III meshes which had to be withdrawn from incontinence and prolapse surgery due to a high erosion and infection rate[6]. If used in pelvic floor surgery these tapes tended to extrude into the vagina where they behaved like a wick drawing vaginal secretions up the entire course of the mesh. Microbiologically this resulted in polymicrobial infections with Gram positive and negative bacteria, anaerobes and aerobes leading to severe complications.

The difference in behaviour of meshes was demonstrated in a series of laboratory experiments in rats.[12] During these experiments it was observed that the Type II and Type III meshes set up a chronic inflammatory response with the formation of giant cells. This never progressed to a stable state with fibrous deposition as one would see with a Type I mesh. As a consequence of the chronic inflammatory response the mesh soon became encapsulated with very little vascularisation thus limiting even further its ability to withstand infection.

Mersilene® (Type III mesh) has been used in a clinical study looking at repair of vaginal prolapses. In this study the patient underwent a sacrocolpopexy with the mesh being introduced either abdominally or vaginally. Results showed that the group where the tape had been introduced abdominally showed a 3% erosion rate, whilst those women in whom the tape had been introduced vaginally exhibited a 20% erosion rate. This was interpreted to show that as well as the structure of the mesh, the environment it is exposed to also has a role to play[13].

A series of simple laboratory experiments demonstrated clearly that Mersilene® had very pronounced capillary and fluid absorbing properties which aided the propagation of Staphylococcus (a bacterium usually considered immobile) from an infected chamber to a sterile one. This did not occur with monofilament suture. The hypothesis therefore is that a suture constructed from Mersilene® would magnify these findings[14,15]. Supporting evidence for this was

provided by the Dalkon shield, a contraceptive intrauterine device composed of a braided thread, which was found to cause pelvic infections in a disproportionately large percentage of its users before being withdrawn from the market[16].

Most surgeons began to convert to monofilament sutures at this time[17], and all of the Type II and Type III products are nowadays used rarely in a clinical setting.

The FDA has issued warnings about mesh products, especially Type II and Type III. Complications associated with the mesh insertion in incontinence and pelvic floor surgery, such as extrusion and infection, led to clear recommendations from Royal College of Obstetrics and Gynaecology to issue guidance on when, how and by whom the mesh should be inserted and removed[17]. NICE guidance supports the use of mesh in some surgical procedures provided that the normal arrangements for consent, audit and clinical governance are in place[18]. Nonetheless, mesh is considered to be a medical device and so any complications should be reported to Medicines and Healthcare products Regulatory Authority (MHRA).

1.4.3 Use of braided sutures in cerclage

There is a paucity of evidence concerning the use of Mersilene® in the context of cervical cerclage and the nature of the suture used is often determined by the surgeon's personal preference. Some surgeons opt to use a non-braided monofilament sutures for cerclage. Conversely detractors suggest that monofilament sutures are not as strong and can potentially traumatise the cervix at insertion. However, these claims are not substantiated by any scientific or clinical evidence.

With its braided nature Mersilene® is proposed to stimulate a chronic inflammatory response and the suture becomes encapsulated. This means that after the securing knot is cut, the lack of fibroblast infiltration results in the easy withdrawal of the suture from the cervical tissue.[14,15]

However, there is some evidence that Mersilene® also has pronounced capillary and absorbent properties and so may act as a wick. This wick may provide an environment where bacteria can grow and a route by which they can migrate and enter the uterus where they may cause a chronic infective state and stimulate early labour. This suspected wicking is prompting many specialists to move towards the adoption of monofilament sutures.

However, some surgeons claim that non-braided sutures are not as strong as braided sutures and increase cervical trauma at insertion. Type I (single strand) material does not set up a chronic immune response, and at removal has been found to be incorporated tightly into its surrounding tissue. That this material has been assimilated can make it extremely difficult to remove without causing significant tearing and damage. Obstetricians and other non-urogynaecology specialists have little experience with meshes or tapes so would not have been aware of the potential for the Mersilene® tape to contribute to premature delivery.

1.4.4 Preterm birth and infection

One hypothesis states that preterm labour is results from an increased susceptibility to infection, and it is recognised that both low-grade chronic and acute infections are risk factors for PTB.

Women who suffer from an insufficient cervix may have an anatomical arrangement which increases the risk of an infective process occurring, thus predisposing them to pre-term labour. In

these women the use of a tape to restore mechanical integrity may inadvertently introduce a route by which an infection stimulates PTB.

1.5. The evidence for effectiveness of the suture material used for cervical cerclage

A comprehensive literature search of MEDLINE, EMBASE, CINHL and ISRCTN from their inception to December 2013 identified no randomised controlled trials comparing the nature of the suture material in relation to planned/elective cerclage. Using search terms of Cerclage, cervix, suture, and Mersilene® suture, the search was extended to non-randomised studies (NRS). Figure 2. Initially, only two published studies were identified to which data has subsequently been supplemented with unpublished data from Prof. Bennett (personal communication). The outcomes considered was pregnancy loss, which included miscarriage and neonatal death.

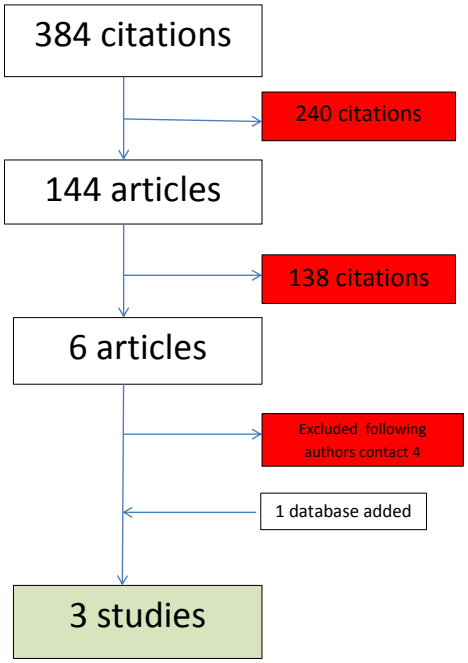
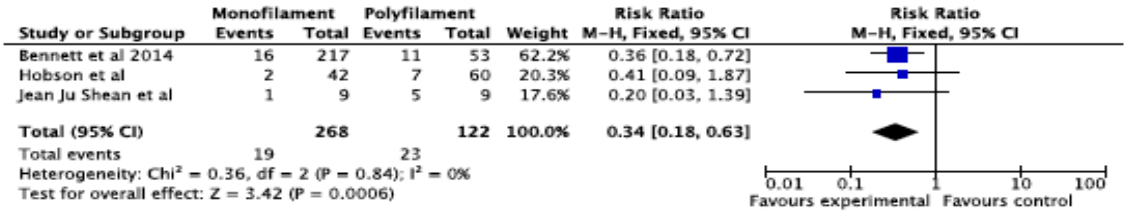


Figure 2 Identification and selection of studies for meta-analysis

The NRS meta-analysis demonstrates that non-braided sutures, compared to braided, were associated with a pregnancy loss rate of 7% compared to 19% respectively (relative risk was 0.34 [95% CI 0.18 to 0.63]). Figure 3.

Figure 3 Non-randomised study meta-analysis of pregnancy loss



1.6. The choice of questions to be asked

1.6.1 Rationale

To date, the effectiveness of the cerclage procedure in the prevention of pregnancy loss remains uncertain [11, 16]. The lack of clear and widely accepted criteria for inserting a cerclage is a possible reason for the inability of the current literature to demonstrate a clinical benefit of cerclage procedures.

Another potential confounding factor, and the hypothesis on which the C-STICH trial is based, relates to the nature of the suture material used. As they were traditionally used at the time it is not unreasonable to assume that the RCTs that provide the data for the Cochrane review used

braided sutures to place a cerclage. If these procedures were performed using a monofilament suture material and the difference in foetal survival identified in our retrospective cohort study between monofilament and braided is true, cervical cerclage may be shown to be a significantly effective procedure.

2. STUDY OBJECTIVE

2.1. Primary objective

To examine the effect of using monofilament suture material compared with braided suture material on pregnancy loss rate in women presenting with an insufficient cervix and treated with cervical cerclage

2.2. Secondary objectives

- To assess the effect of suture material on other pregnancy and neonatal outcomes
- To explore the variation in effect between McDonald's and Shirodkar's cerclage, especially with reference to bladder dissection
- To explore the variation in effect between the indication for cerclage
- To produce advice and a video clip to illustrate best practice in cerclage stitch insertion and removal

3. TRIAL DESIGN

3.1. Design

C-STICH is a multicentre, open, randomised controlled trial.

3.2. Setting

The C-STICH study will run in at least 32 NHS Obstetric Units in UK. Recruitment will be in antenatal clinics, outpatient departments, gynaecology wards. Randomisation and insertion of the cerclage will be performed in antenatal clinics, day surgery areas, surgical in-patient settings and delivery suites.

4. STUDY POPULATION

The target population for C-STICH are women attending antenatal clinics or admitted to gynaecology wards in whom the reviewing clinician believes that the placement of a cervical cerclage is the most appropriate method to prevent a miscarriage or pre-term birth.

These women will be invited to take part in the C-STICH trial at the time the decision is made to undertake a cervical cerclage procedure.

4.1. Eligibility Criteria

4.1.1 Inclusion

- Singleton pregnancy
- Indication for cervical cerclage (any of the below)

- A history of three or more previous midterm losses or premature births (≤ 28 weeks)
- Insertion of cervical sutures in previous pregnancies
- A history of midtrimester loss or premature birth with a shortened (≤ 25 mm) cervix
- Women whom clinicians deem to be at risk of preterm birth either by history or the results of an ultrasound scan

4.1.2 Exclusion

- Women who have taken part in C-STICH previously
- Women aged less than 18 years old at the time of presentation
- Those with a multiple pregnancy
- Those requiring a rescue cerclage
- Women who are unwilling or unable to give informed consent
- Those in whom a cerclage will be placed by any route other than vaginally (e.g. via an abdominal route)

4.2. Identifying potential participants

Cerclage tends to be performed between 12 and 22 weeks gestation. Potentially eligible women will be identified in antenatal clinics, in gynaecology wards or in an emergency setting and invited to join the trial at the time the decision is made to undertake a cervical cerclage.

4.3. Approaching potential participants for consent

Potential participants will only be approached by suitably qualified and experienced personnel whose names appear on the delegation log.

4.3.1 Obtaining consent

All women who are referred to secondary care for cervical cerclage will be screened prior to their antenatal appointment by the C-STICH research nurse or PTB clinic nurse in each centre as a potential participant. The obstetrician or gynaecologist who will be providing the woman's clinical care and performing the procedure will discuss preventative options and establish eligibility based on history and preferences.

For the majority of women, there will be a delay of at least one night before the cerclage procedure is undertaken, allowing adequate time for consideration of participation in the trial. In some circumstances, where a monitoring ultrasound scan shows a shortening cervix without bulging foetal membranes, the cerclage procedure might be performed the same day. In either situation, the indication for the cerclage will be discussed before the trial is introduced.

Consent to participate in C-STICH will be sought by the obstetrician, but the research nurse for the centre may be involved in the consent discussion. Women will be asked to confirm their consent to participate in the C-STICH trial by initialling the appropriate boxes on the consent form and

signing the form in the presence of the person taking consent. Multiple copies will be available to ensure a copy is given to the women; one to be kept in the patient notes, one in the local site file and one sent to the C-STICH Trial Office.

The primary outcome of C-STICH is neonatal mortality at up to one month post-delivery. Rather than contact the trial participant to enquire of their child's mortality, at the end of the trial a list of NHS numbers assigned to the children born to trial participants will be provided to the Health and Social Care Information Centre (HSCIC). The HSCIC will be asked to confirm if a death certificate has been issued against each number, and if so, the date of death. The participant will be made aware of this in the C-STICH Participant Information Sheet and their agreement will be recorded on the consent form.

All women approached should be recorded on the screening log, available in the investigator site file. This information will only be passed to the coordinating centre as an anonymous screening log.

4.3.2 Informing the participant's GP

Following the participant granting consent, her GP will be notified and a template "Letter to GP" is supplied.

4.4. Ineligible patients

If a woman is screened but is not eligible for the trial, be it due to a preference for the use of a particular suture type, a contraindication, a pathological reason, or consent for randomisation is not given, an anonymous record of the case should be kept in the screening log. The screening log will collect hospital number, age group, ethnic group, and the reason each patient is not eligible to participate in the trial. Women who consent and are subsequently found to be ineligible will be noted.

The screening log should be kept in the site file and a copy sent to the C-STICH Trial Office on a monthly basis. The members of the trial co-ordination team will be unable to identify women based on the information provided. This screening log information will inform updates to the funder regarding recruitment targets for C-STICH Trial.

4.5. CO-ENROLMENT

Women randomised to the C-STICH trial should be excluded from participation in any further trial of investigational medicinal products (IMPs) or procedures for the prevention of second trimester miscarriage or pre-term birth. If the woman does not undergo a cerclage after randomisation, but is still contributing to data collection, any further treatments within trials for prevention of PTB should be noted.

Women already participating in another trial of an IMP or procedure for prevention of second trimester miscarriage or PTB are able to participate in C-STICH.

5. RANDOMISATION

The participant should be randomised just prior to the cervical cerclage procedure, to minimise the number of withdrawals and protocol violations, but allowing sufficient time for the obstetrician to prepare the sutures for the procedure.

5.1. Randomisation

Birmingham Clinical Trials Unit will provide a bespoke web-based randomisation with telephone back-up. Patients are entered and randomised into the trial by logging into secure online webpage available at www.birmingham.ac.uk/CSTICH. Each person eligible to randomise will be provided with a unique username and password. The online randomisation is available 24 hours a day, 7 days a week apart from short periods of scheduled maintenance and when there are occasional network interruptions. Alternatively, investigators can make one Freephone telephone call (Tel - 0800 953 0274) to the randomisation service. This telephone randomisation service is available between 0900 – 1700 hrs Monday to Friday.

Randomisation Forms will be provided to investigators and may be used to collate the necessary information prior to randomisation. All questions and data items on the Randomisation Form will need to be answered before a trial number and allocation can be given. If an essential data item is missing, randomisation will be suspended but can be resumed once the information is available. Only when all eligibility criteria and baseline data items have been provided will a trial number and treatment allocation be given. This will be followed by a confirmatory email sent to the randomising investigator, local Principal Investigator and the research nurse.

A minimisation procedure using a computer-based algorithm will be used to avoid chance imbalances in treatment allocation and the following potentially important variables:

- Indication for the cerclage (history / ultrasound)
- Technique planned (With or without bladder dissection)
- Intention to commence patient on progesterone (yes / no)
- Randomising centre

To avoid any possibility of the treatment allocation becoming too predictable, we will include a random factor within the algorithm. This factor will force a proportion of the allocations (1 in 5) to be a true randomisation rather than a minimised allocation.

6. TREATMENT ALLOCATIONS AND PREGNANCY MANAGEMENT

6.1. Trial treatment

Depending on the results of the randomisation, cerclage will be performed with either a monofilament or braided suture.

Both types of suture used in C-STICH are standard surgical materials already in use. There are various suture brands available and CE marked for this purpose, but the most commonly used are Mersilene® a nonabsorbable, braided, sterile surgical suture composed of poly-ethylene terephthalate and Ethilon, a nonabsorbable, monofilament, sterile surgical suture composed of the long-chain aliphatic polymers Nylon 6 and Nylon 6,6.

The MHRA have confirmed that C-STICH is not classed as a device trial.

6.2. Cerclage technique

The technique of suture insertion (i.e. with or without bladder dissection) will be at the surgeon's discretion as long as suture is not totally buried. To ensure the groups are balanced as evenly as

possible, the proposed cerclage technique will be taken into account in the allocation of the type of suture used, so this must be decided before randomisation.

A high vaginal swab should be taken at the time the cerclage is placed. This swab will be sent to the local microbiology department, where a Gram stain and aerobic and anaerobic culture will be undertaken. The presence or absence of a panel of potentially pathogenic microorganisms will be recorded in standardised fashion on the study Microbiology Transfer Form. Microbiology Departments will follow their local SOPs when issuing clinical reports of results.

6.3. Other management at discretion of local doctors

Apart from the trial treatments allocated at randomisation, all other aspects of PTB prevention management e.g. progesterone will be at the discretion of the care-providing clinician.

The pregnancy should be managed as per current usual practice for women with a cerclage *in situ*, with no other special treatments, no special investigations, and no extra follow-up visits outside those required clinically.

6.4. Withdrawal of treatment or protocol violation

Whilst a participant may voluntarily withdraw from this study at any time, it is impossible to change the allocated treatment once the cerclage procedure has been performed as it would be unsafe and unethical to remove and replace the suture thread.

Unless withdrawn from the study, if a participant does not return for a standard antenatal appointment, attempts will be made to contact her to collect pregnancy outcomes and adverse events. If a woman decides, after randomisation, she does not wish to have the cerclage, or the randomly allocated suture, she may withdraw herself from the trial treatment. The timing of randomisation as close as possible to the procedure should minimise the number of post-randomisation withdrawals or violations.

Clear distinction will be made as to whether a participant is withdrawing from the trial but will still be followed up on an intention-to-treat basis, or whether the participant refuses any follow-up. If a participant explicitly withdraws consent to have any further data recorded their decision will be respected and recorded. All communication surrounding the withdrawal will be noted in the patient's hospital records and trial database, and no further data will be collected for that participant.

Should a women lose capacity to provide continued consent, they will be assumed to wish to remain in the C-STICH trial as there would be no further procedures or tests required for the trial.

6.5. Removal of cerclage suture

Planned removal of the suture would occur at 37 (± 1 week) weeks' gestation and the suture will be removed by the method the clinician feels most appropriate.

Upon removal, the suture will be sent to the local microbiology laboratory for aerobic and anaerobic culture. The presence or absence of a panel of potentially pathogenic microorganisms will be recorded in standardised fashion on the study Microbiology Transfer Form. Most Microbiology laboratories would not routinely process suture material, and we do not expect that

it will be necessary to issue a clinical report of the culture result. Where a local laboratory chooses to do so, they should follow their local SOP for reporting of results.

6.6. Blinding of suture type at cerclage

The obstetrician performing the cerclage cannot be blinded to the nature of the thread used. However, we intend not to record the suture type in the hand-held maternity notes.

7. FOLLOW-UP AND OUTCOME MEASURES

7.1. Primary outcome measure

- Pregnancy loss rate (miscarriage and perinatal mortality, including any still birth or neonatal death in the first week of life)

7.2. Secondary outcome measures

7.2.1 Maternal

- Gestation at delivery
- Mode of initiation of labour
- Mode of delivery
- Adverse events: suture related cervical tears, chorioamnionitis, maternal pyrexia of 38°C, systemic infection requiring antibiotics (infection parameters based on Centre for Disease Control / National Healthcare Safety Network [CDC / NHSN] guidance)

7.2.2 Neonatal

- Late neonatal death, defined as a death beyond 7 days and before 28 days after delivery.
- Length of stay in neonatal unit (including level of care)
- Severe abnormality on cranial ultrasound scan
- Oxygen dependency at 36 weeks corrected gestation
- Necrotising enterocolitis (Bell's stage 2 or 3)
- Retinopathy of prematurity requiring laser treatment

7.2.3 Microbiological

Full cultures will be undertaken to identify the complete range of potentially pathogenic bacteria isolated from the suture, and high vaginal area. The likely significance of microorganisms isolated from each clinical sample will be assessed in the context of clinical evidence of infection in the mother and her baby.

8. DATA COLLECTION FORMS

Data for the purpose of assessing the efficacy and safety within the C-STICH trial will be collected from the clinical team responsible for the participants care on a number of data collection (case report) forms. Data required for the primary and the majority of secondary outcomes are

objective measures which are routinely collected for clinical purposes and will be transcribed from patient records.

The data collection forms will be either be completed in paper form and returned to the C-STICH Trial office by post, or can be entered directly onto the database by those with on-line access. The patient's GP details, NHS, and hospital number will be collected and all may be used in the process of collecting missing data.

8.1.1 Clinical Assessment Form

At the first clinic visit, the gynaecological and obstetric clinical history of the woman will be taken. Details of ultrasonographic assessments will be collected alongside basic demographic details.

8.1.2 Randomisation Form and Screening Log

The Randomisation Form is a checklist for eligibility and key prognostic details needed for minimisation within the randomisation. This is completed by the investigator or C-STICH research nurse before randomisation.

The Screening Log will record basic details of all women approached, including those who are found to be ineligible and those that decline their invitation to participate. This should be kept up to date by the C-STICH research nurse.

8.1.3 Cerclage Procedure Form

The local approved clinician will report on the cerclage procedure using a standardised report form, This will record a number of items including the technique used, the suture thread used, the number of "bites", the position of any knots, and use of any tocolytic agent.

8.1.4 Pregnancy Outcome Form

At the conclusion of the pregnancy, the primary outcome and secondary maternal outcomes will be collected.

8.1.5 Neonatal Outcome Form

For all babies who are admitted to the neonatology unit, core neonatal outcomes related to prematurity will be collected.

Late neonatal death will be flagged using the babies NHS / CHI number. See section 10.3 for further details.

8.1.6 Serious Adverse Event Form

This will collect details of all SAEs are defined and description in Section 9.

8.1.7 Microbiology Assessment Form

Data forms pertinent to the assays and analyses being undertaken on the swabs and suture thread taken for the sub-study will be used to standardise the data collected.

8.2. Source data

For the purposes of the C-STICH trial, source data comprises of:

- Clinical notes
- High vaginal swabs and the removed sutures or other material used for microbiological analysis.

8.3. Blinding of assessment

Whilst obstetricians cannot be blinded to the allocation, all attempts will be made to blind those collecting the outcomes to the type of suture used. The email confirmation of suture allocation will not be kept in the medical notes. The patient, microbiologists, neonatologists and other members of the clinical team responsible for the woman's care will be blinded to the allocation.

8.4. Health economic outcomes

In view of the similarity in prices of suture material used in the trial, the fact that the surgical procedure used for inserting both suture materials is identical, and the high cost of care of pre-term babies, any difference in pregnancy loss rate is going to dominate an economic evaluation. However, the primary and secondary outcomes collected will provide enough information to assess any potential cost saving of one type of suture material over the other if a difference is identified.

9. SAFETY MONITORING PROCEDURES

There may be unexpected serious adverse reactions associated with monofilament or braided sutures when used in cervical cerclage. Monofilament or braided sutures have been used to treat cervical cerclage for many years and there is no reason to believe there are adverse biochemical reactions intrinsic to the material of the suture thread, but there may be adverse events arising from the biomechanical properties of the thread. There are also known adverse events of cerclage irrespective of suture material used.

This protocol distinguishes adverse events from outcomes.

It is the responsibility of investigators to notify adverse events to the C-STICH Trial Office, who will forward these to the sponsor. It is the remit of the sponsor to report to the ethics committee. It is therefore imperative that all investigators have a thorough understanding of anticipated adverse events and the reporting process of these events.

9.1. General Definitions

Adverse Events (AE)

An AE is:

- Any unintentional, unfavourable clinical sign or symptom. This will include complications of cervical cerclage, namely:
- Severe cervical lacerations at time of procedure.
- Any new illness or infection or the deterioration of existing disease or illness
- Any clinically relevant deterioration in any laboratory assessments or clinical tests, for example continued shortening of the cervix or dilatation.

The following are not AEs:

- A pre-existing condition (unless it worsens significantly during pregnancy).
- Diagnostic and therapeutic procedures, such as removal of the cerclage stitch or repeated ultrasound assessments.

Expected adverse events from cerclage include:

- Cervical laceration or amputation at delivery from scar tissue that forms on the cervix.
- Bladder injury as a result of the cerclage procedure
- Cervical dystocia, where the cervix fails to dilate during labour

Serious Adverse Events (SAEs)

An SAE is an untoward event which:

- Results in death
- Immediately threatens the life of participant*
- Results in hospitalisation or a longer than anticipated stay in hospital
- Results in a persistent or significant disability

*Life-threatening in the definition of a serious adverse event refers to an event in which the mother was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. Important adverse events that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the pregnancy or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

As cerclage is performed after organogenesis, any congenital anomalies are not attributable to the trial intervention and are not considered an SAE.

Events NOT considered to be SAEs are hospitalisations for:

- routine monitoring or removal of cervical cerclage more than 48 hours after the procedure

- treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the pregnancy
- admission to a hospital for delivery of the baby
- management of a premature baby

Expected SAEs

Expected SAEs also include, but are not limited to, the following:

- Premature rupture of membranes within 48 hours of the procedure
- Infection of the amniotic sac (chorioamnionitis) requiring intravenous antibiotics.
- Preterm labour or miscarriage within 24 hours of cerclage.
- Other conditions threatening the life of the mother

A miscarriage, preterm delivery or neonatal death 48 hours after the cerclage procedure will be considered an outcome and not an adverse event, and should be reported according to Section 8.1.4 (Pregnancy outcome form).

9.2. Reporting AEs

All adverse events, from the day of the cerclage procedure until 28 days after the birth of the baby, or until the baby is discharged from hospital care (whichever arrives first), whether observed directly or reported by the patient, will be collected and recorded. Non-serious adverse reactions or events are not required to be reported in an expedited manner, but will be recorded on the data collection forms.

9.3. Reporting SAEs

All SAEs must be recorded on a SAE Form and faxed to BCTU on 0121 415 9136 within 24 hours of the research staff becoming aware of the event. The Principal Investigator (or other nominated clinician) has to assign seriousness, causality and expectedness to the SAE before reporting. All SAEs should be assessed for seriousness, causality and expectedness.

For each SAE, the following information will be collected:

- full details in medical terms with a diagnosis, if possible
- its duration (start and end dates; times, if applicable)
- action taken
- outcome
- causality, in the opinion of the investigator*
- whether the event would be considered expected or unexpected* (using the principles described above)

*Assessment of causality and expectedness must be made by a doctor. If a doctor is unavailable, initial reports without causality and expectedness assessment should be submitted to BCTU by a

healthcare professional within 24 hours, but must be followed up by medical assessment as soon as possible thereafter, ideally within the following 24 hours.

The local investigator and others responsible for patient care should institute any supplementary investigations of SAEs based on their clinical judgement of the likely causative factors and provide further follow-up information as soon as available. If a participant dies, any post-mortem findings must be provided to BCTU. BCTU will report all deaths to the DMEC for continuous safety review.

SAEs still present beyond 28 days post-partum must be followed up until the final outcome is determined.

BCTU will report all SAEs to the DMEC following a timetable agreed by the DMEC prior to study commencement. The DMEC will review these data blinded to treatment allocation but will be able to review unblinded data if necessary. BCTU will also report all SAEs to the main REC annually, and to the Trial Steering Committee following a timetable agreed by the TSC prior to study commencement. Local Investigators are responsible for reporting SAEs to their host institution, according to local regulations, but they do not need to inform the main REC as this will be done by BCTU as detailed above.

9.4. Notification of deaths

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

All miscarriages, stillbirths and neonatal deaths to 28 days post-partum are outcomes and should be reported as such. Miscarriages, still births or neonatal deaths within 48 hours of the cerclage procedure should also be reported as SAEs.

9.5. Safety reporting responsibilities

Local Principal Investigator (or nominated individual in PI's absence):

- To record **all** AEs that occur in the women taking part in the trial. This includes non-serious, serious, expected or unexpected adverse events, unless defined as outcomes above.
- Medical judgement in assigning seriousness, expectedness and causality to AEs.
- To fax SAE forms to BCTU within 24 hours of becoming aware, and to provide further follow-up information as soon as available.
- To report SAEs to local committees if required, in line with local arrangements.
- To sign an Investigator's Agreement accepting these responsibilities.

Chief Investigator (or nominated individual in CI's absence):

- To assign causality and expected nature of SAEs where it has not been possible to obtain local assessment.
- To review all events assessed as SAEs in the opinion of the local investigator.

Birmingham Clinical Trials Unit:

- To prepare annual safety reports to the main REC and TSC.
- To prepare SAE safety reports for the DMEC following a timetable agreed by the DMEC prior to study commencement, or as requested by the DMEC.
- To report all fatal SAEs to the DMEC for continuous safety review.

Trial Steering Committee (TSC):

- To provide independent supervision of the scientific and ethical conduct of the trial on behalf of the Trial Sponsor and funding bodies.
- To review data, protocol deviations, outcome capture rates, adverse events (during treatment and up to the end of follow-up).
- To receive and consider any recommendations from the DMEC on protocol modifications.

Data Monitoring & Ethics Committee (DMEC):

- To review (initially at approximately six-monthly intervals) overall safety and morbidity data to identify safety issues which may not be apparent on an individual case basis.
- To recommend to the TSC whether the trial should continue unchanged, continue with protocol modifications, or stop.

10. DATA MANAGEMENT

10.1. Clinical Data

Data from the Case Report forms described in Section 8 should be entered into the secure online C-STICH database as soon as possible after collection by the research nurse, investigator or microbiologist. These clinical personnel will be allocated personal usernames and passwords that only allow access to the trial participants being treated at their site. Alternatively, paper forms can be sent to the C-STICH Trial Office for central input.

Data validation is built into the online database. Range, date and logic checks are performed at the point of data entry. Email reminders will be sent to the research nurses for missing data forms, missing data or data inconsistencies.

10.2. Embedded microbiological sub-study

10.2.1 Specimen identification, processing and storage

High vaginal swabs will be delivered to each participating hospital's local diagnostic microbiology laboratory where they will be processed in accordance with local standard operating procedures for routine processing of swabs or tissue. The Microbiology transfer form includes a list of microorganisms that Microbiology Departments will be expected to identify in samples; this will ensure that there is consistency between centres in reporting the presence of bacteria that are not unequivocal pathogens.

Most laboratories would not routinely process suture materials. Laboratories will be asked to place the suture in 3-5 mL of sterile 0.9% saline. After sonication, 0.1 mL volumes will be cultured on appropriate agar plates for culture for aerobic and anaerobic bacteria and fungi.

10.2.2 Quality Assurance of Microbiological Assessments

We will confirm that all contributing microbiology laboratories participate in an external quality assurance scheme and are accredited by CPA (UK) Ltd., UKAS, or another equivalent body.

10.2.3 Long-term storage of data

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

Principal Investigators are responsible for the secure archiving of essential trial documents for their site, according to the local policy at that site. All essential documents will be archived for a minimum of 5 years after completion of trial.

10.3. Long-term follow-up

Neonatal outcomes will be determined six months after the last child born to a trial participant is discharged from hospital care. The C-STICH post-natal information form will ask "Was this baby alive at 28 days after birth?" with the answers of either 'Yes', 'No', or 'Discharged before this time.' This means that only those neonates marked as 'Discharged before this time' need to be followed up.

A number of methods will be used to follow up the clinical outcome of these children. The NHS number of the neonates will be recorded. At the appropriate time point the NHS numbers assigned to those of children denoted as 'Discharged before this time' will be submitted to the Office of National Statistics (ONS) with a request for any death outcomes associated with these numbers. Should the ONS not be able to supply a complete outcomes dataset then the mothers GP will be contacted and local / regional mortality databases consulted.

10.4. Definition of the End of Trial

The study will be deemed complete when the last recruited woman has delivered and, if applicable, her baby is discharged from hospital care.

11. ACCRUAL AND ANALYSIS

11.1. Sample size

The sample size for C-STICH is informed by our meta-analysis (section 1.5) with some allowance made for the fact that this evidence is non-randomised. Here, the pregnancy loss rate was 7.1% with monofilament sutures compared to 19% with braided sutures, a reduction of 66% (RR: 0.34, 95%CI: 0.18 to 0.63; figure 1). A total sample of 326 women would be enough to detect a difference of this size (with 90% power and p=0.05), but we have inflated this to a total sample target of 900 (gaining full outcome data on 878) which will enable us to detect a more plausible relative reduction of 41% (19% with braided to 11.2% with monofilament) with 90% power (p=0.05).

If the control rate of pregnancy loss in the braided group is lower than 19% then we still have reasonable power to detect this same relative difference of 41% provided the rate of pregnancy loss is at least 11% (Table 2)

Table 2 Power calculation for C-STICH for various levels of pregnancy loss rate in the primary outcome.

For a relative reduction of 41% (n=878)				
Rate in monofilament group	Rate in braided group	Absolute risk reduction	NNT	Power (p=0.05)
0.112	0.190	0.078	12.8	90%
0.100	0.170	0.070	14.3	86%
0.088	0.150	0.062	16.1	81%
0.077	0.130	0.053	18.9	73%
0.065	0.110	0.045	22.2	66%
0.053	0.090	0.037	27.0	57%

The control group rate of pregnancy loss will be monitored throughout the pilot and full study in conjunction with the DMEC to see how this may affect the sample size calculations. The DMEC will be given the remit of advising if our sample size would need to be altered based on this information.

11.2. Projected accrual and attrition rates

Hospital Episode Statistics data indicates that there are about 1950 procedures performed in England each year, from which you could extrapolate to estimate 2300 women per year in the UK as a whole undergo cerclage. Assuming 25% of these are ineligible, and assuming only 60% of the eligible women are approached and 50% of those consent, it is feasible to recruit 900 women in 30 months.

To account for a realistic staged trial set up in participating units and to mitigate the risk of any unexpected delays or barriers to recruitment, recruitment will proceed over 30 months. There will be an internal pilot of 9 months, recruiting from 8 lead centres, which are expected to recruit 2 participants per month each. If the pilot is successful, C-STICH would expand to recruit from at least 24 more centres and would require these centres each to recruit an average of 0.75 participants per month (8 women per year).

11.3. Statistical Analysis

The analysis will be by intention to treat. Every attempt will be made to gather data on all women randomised and their babies, irrespective of compliance with the treatment protocol. Point estimates, 95% confidence intervals and *p*-values from two-sided tests will be calculated. A comprehensive Statistical Analysis Plan will be drawn up prior to any analysis and provide to the independent Data Monitoring Committee (DMEC) for review.

11.3.1 Primary analysis

We will use a log-binomial regression model to calculate the relative risk and 95% confidence of the primary outcome (pregnancy loss defined as miscarriage or perinatal mortality). Minimisation variables (see section 5.1) will be included in the model as covariates. The statistical significance of the treatment group variable will be determined by an associated chi-squared test.

11.3.2 Secondary analysis

Dichotomous secondary outcomes (e.g. infection, cervical tears, late neonatal death) will be analysed in the same fashion as the primary outcome. Time from conception to delivery and randomisation to delivery (censoring for pregnancy loss) will be analysed by log-rank test with a Cox Proportional Hazard (PH) model built if the assumptions of proportionality are met. Standard methods will be used to analyse other outcome (e.g. chi-squared test for mode of delivery). Appropriate summary statistics split by group will be presented for each outcome (e.g. proportions/percentages, mean/standard deviation or median/interquartile range).

11.3.3 Sub-group analyses and missing data

Subgroup analyses will be limited to the same variables which were used as minimisation variables (listed in section 5.1). Tests for statistical heterogeneity (e.g. by including treatment group by subgroup interaction parameter in the regression model) will be performed prior to any examination of effect estimate within subgroups. Sensitivity analyses will be performed on the primary outcome to investigate the impact of any missing data, e.g. assuming pregnancy loss for missing outcomes. Methods using multiple imputation (MI) will also be incorporated.

11.3.4 Timing of assessments

An interim report including the analysis of major endpoints will be provided in strict confidence to a Data Monitoring Committee at intervals of at least 12 months, or to a timetable agreed by the DMEC prior to study commencement (see Section 12.5 for further details on trial data monitoring including the use of pragmatic stopping criteria). Final analysis will be performed once all live babies have reached 28 days of life and the database has been cleaned and locked.

12. DATA ACCESS AND QUALITY ASSURANCE

12.1. Confidentiality of personal data

Personal and sensitive data will be collected directly from trial participants' hospital notes. Participants will be informed about the transfer of this information to the C-STICH Study Office at BCTU and asked for their consent. With the patient's consent, their full name, date of birth, National Health Service (NHS) or Community Health Index (CHI) number of both mother and baby, Hospital number, general practitioner (GP) details will be securely stored on the trial database. This will enable tracing of women who deliver in a different hospital.

Patients will be identified using only their unique trial number to verify identify on the data collection forms and in any correspondence between the C-STICH Study Office and the participating site.

Consent forms will be collected by the C-STICH Study Office and stored securely in the Trials Master File (TMF). These forms will be available to various regulatory bodies for inspection upon request.

Data collected will be entered onto a secure computer database, either directly by the local site *via* the internet using secure socket layer (SSL) encryption technology, or indirectly from paper forms by C-STICH study office staff. Access control will ensure that local trials staff will only be able to view information relating to participants at their site.

All personal information received in a paper format for the trial will be held securely in locked filing cabinets in a safe haven office and treated as strictly confidential according to BCTU policies.

All staff involved in the C-STICH study, be they clinical, academic, or employees of BCTU, share the same duty of care to prevent unauthorised disclosure of personal information. No data that could be used to identify an individual will be published. Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 1998 and any amendments.

12.2. In-house Data Quality Assurance

12.2.1 Monitoring and Audit

This study may be monitored to ensure compliance with GCP. A risk proportionate approach to the initiation, management and monitoring of the study will be adopted and outlined in the study-specific risk assessment.

12.2.2 Direct Access to Source Data

Investigators and their host Trusts will be required to permit trial-related monitoring and audits to take place by the C-STICH Trial Coordinator, providing direct access to source data and documents as requested. The trial site may also be subject to audit by the Research and Development Manager of their own Trust, or monitoring by the sponsor, and should do everything requested by the Chief Investigator in order to prepare and contribute to any inspection or audit. Trial participants will be made aware of the possibility of external audit of data they provide in the participant information sheet.

12.2.3 Statistical monitoring throughout the trial

The study will also adopt a centralised approach to monitoring data quality and compliance. A computer database will be constructed specifically for the trial data and will include range and logic checks to prevent erroneous data entry. Independent checking of data entry will be periodically undertaken on small sub-samples. The trial statistician will regularly check the balance of allocations by the stratification variables.

12.3. Definition of a serious breech

A serious breach is that which is likely to effect to a significant degree:

1. the safety or physical or mental integrity of the participants of the trial; or

2. the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or BCTU, the C-STICH Trial Office must be notified within 24 hours. It is the responsibility of the Chief Investigator to determine whether the incident constitutes a serious breach and if so, to assess the impact of the breach on the scientific value of the trial. BCTU will report serious breaches to the sponsor and to the research ethics committees as necessary.

12.4. Independent Trial Steering Committee

The TSC provides independent supervision for the trial, providing advice to the Chief and Co-Investigators and the sponsor on all aspects of the trial and affording protection for patients by ensuring the trial is conducted according to the guidelines for Good Clinical Practice.

If the Chief and Co-Investigators are unable to resolve any concern satisfactorily, Principal Investigators, and all others associated with the study may write, through the Trial Office, to the chairman of the TSC drawing attention to any concerns they may have about the possibility of particular side-effects, of particular categories of patient requiring special study, or any other matters thought relevant.

12.5. Data Monitoring and Ethics Committee: determining when clear answers have emerged

If one treatment really is substantially better or worse than any other with respect to the primary outcome, then this may become apparent before the target recruitment has been reached. Alternatively, new evidence might emerge from other sources that any one treatment is definitely more, or less, effective than any other. To protect against this, during the main period of recruitment to the study, interim analyses of the primary outcome and adverse events will be supplied, in strict confidence, to an independent Data Monitoring and Ethics Committee (DMEC) along with updates on results of other related studies, and any other analyses that the DMEC may request. The DMEC will advise the chair of the TSC if, in their view, any of the randomised comparisons in the trial have provided both (a) “proof beyond reasonable doubt” that for all, or for some, types of patient one particular treatment is definitely indicated or definitely contraindicated in terms of a net difference in the major endpoints, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results. The TSC can then decide whether to close or modify any part of the trial. Unless this happens, however, the TMG, TSC, the investigators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results.

The BCTU Trial office will forward open DMEC meeting minutes to the Sponsor and funding Body.

Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least $p<0.001$ (similar to a Haybittle-Peto stopping boundary) in an interim analysis of a major endpoint may be needed to justify halting, or modifying, the study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed.

12.6. Long-term storage of data

Archiving will be authorised by BCTU on behalf of the Sponsor following submission of the end of trial report. Destruction of essential documents will require authorisation from the BCTU on behalf of the Sponsor.

Principal Investigators are responsible for the secure archiving of essential trial documents for their site, according to the local policy at that site. All essential documents will be archived for a minimum of 5 years after completion of trial. Destruction of essential documents will require authorisation from BCTU on behalf of the Sponsor.

Trial data will be stored under controlled conditions for at least 3 years after closure. This will allow adequate time for review and reappraisal, and in particular with the C-STICH trial, form the basis for further follow-up research. Any queries or concerns about the data, conduct or conclusions of the trial can also be resolved in this time. Long-term offsite data archiving facilities will be considered for storage after this time. BCTU has standard processes for both hard copy and computer database legacy archiving, including anonymisation of trial data.

13. ORGANISATION AND RESPONSIBILITIES

To ensure the smooth running of the trial and to minimise the overall procedural workload, it is proposed that each participating centre should designate individuals who would be chiefly responsible for local co-ordination of clinical and administrative aspects of the trial.

All investigators are responsible for ensuring that any research they undertake follows the agreed protocol, for helping care professionals to ensure that participants receive appropriate care while involved in research, for protecting the integrity and confidentiality of clinical and other records and data generated by the research, and for reporting any failures in these respects, adverse reactions and other events or suspected misconduct through the appropriate systems.

13.1. Centre eligibility

Centres will be eligible to participate in C-STICH if they routinely perform cervical cerclage with or without bladder dissection, are prepared to randomise between monofilament and braided cerclage sutures, and have microbiology facilities which are able to perform cultures and bacterial profiles from swabs and sutures.

13.2. Local Co-ordinator at each centre

Each Centre should nominate an obstetrician to act as the local Principal Investigator and bear responsibility for the conduct of research at their centre. Close collaboration between all clinical teams is particularly important in C-STICH in order that patients for whom cervical cerclage is an appropriate treatment option can be identified sufficiently early for inclusion in the trial.

The local Principal Investigator is responsible for the overall conduct of the study at the site and to ensure compliance with the protocol and any amendments. In accordance with the principles of International Committee on Harmonisation Good Clinical Practice Guidelines (ICH GCP) the following areas listed in this section are also the responsibility of each Investigator. Responsibilities may be delegated to an appropriate member of study site staff. Delegated tasks

must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

- to ensure that all medical and nursing staff involved in the care of women with cervical insufficiency are well informed about the study and trained in trial procedures
- to ensure written informed consent is obtained before randomisation
- to designate or recruit a C-STICH research nurse
- to be responsible for the quality of data recorded in the data collection forms at their site
- to maintain their site's Investigator Site File
- to sign the Investigator's Declaration in the Clinical Study Site Agreement
- to ensure all study staff hold evidence of appropriate GCP training
- to ensure confidentiality of all trial data collected
- to report to the C-STICH Trial Office all SAEs in a timely manner
- to report any protocol violations and suspected serious breaches to the C-STICH trial office

13.3. Research Nurse at each centre

Each participating centre should also designate one nurse as local Nursing Coordinator. This person would be responsible for ensuring that all eligible patients are considered for the study, that patients are provided with study information sheets, and have an opportunity to discuss the study if required. The nurse may be responsible for collecting the baseline patient data and for administering the follow-up evaluations. This person would be sent updates and newsletters, and would be invited to training and progress meetings.

13.4. The C-STICH Trials Office at BCTU

The C-STICH Trial Office at BCTU is responsible for providing all trial materials, including the trial folders containing printed materials and the update slides. These will be supplied to each collaborating centre after all relevant approvals have been obtained. Additional supplies of any printed material can be obtained on request. The Trial Office also provides the central randomisation service and is responsible for collection and checking of data (including reports of serious adverse events thought to be due to trial treatment), for reporting of serious and unexpected adverse events to the sponsor and/ or regulatory authorities and for analyses. The Trial Office will help resolve any local problems that may be encountered in trial participation.

13.5. Research Governance

The conduct of the trial will be according to the principles of the International Committee on Harmonisation, Good Clinical Practice Guidelines (ICH GCP).

All centres will be required to sign an Investigator's Agreement, detailing their commitment to accrual, compliance, Good Clinical Practice, confidentiality and publication. Deviations from the agreement will be monitored and the TSC will decide whether any action needs to be taken, e.g. withdrawal of funding, suspension of centre.

The Trial Office will ensure researchers not employed by an NHS organisation hold an NHS honorary contract for that organisation.

13.6. Regulatory and Ethical Approval

13.6.1 Ethical and Trust Management Approval

The Trial has a favourable ethical opinion from Norwich and Norfolk' Multi-centre Research Ethics Committee (MREC), confirming that the trial design respects the rights, safety and wellbeing of the participants.

The Local Comprehensive Research Network will conduct governance checks and assess the facilities and resources needed to run the trial, in order to give host site permission. The Trial Office is able to help the local Principal Investigator in the process of the site specific assessment by completing much of Site Specific Information section of the standard IRAS form as possible. The local Principal Investigator will be responsible for liaison with the Trust management with respect to locality issues and obtaining the necessary signatures at their Trust.

As soon as Trust approval has been obtained, the Trial Office will send a folder containing all trial materials to the local Principal Investigator. Potential trial participants can then start to be approached.

Within 90 days after the end of the study, the Chief Investigator, on behalf of the Sponsor, will ensure that the MREC is notified that the study has finished. If the study is terminated prematurely, those reports will be made within 15 days after the end of the study.

The Chief Investigator will supply the Sponsor with a summary report of the clinical study, which will then be submitted to the MREC within one year after the end of the study.

13.7. Funding and Cost implications

The research costs of the trial are funded by a grant from the NIHR Health Technology Assessment Programme awarded to the University of Birmingham.

The trial has been designed to minimise extra 'service support' costs for participating hospitals, with no extra visits to hospital and no extra tests. Additional costs service support costs associated with the trial, e.g. identifying potential participants, gaining consent, are estimated in the Site Specific Information section of the standard IRAS form. These costs should be met by accessing the Trust's Support for Science budget *via* the Local Comprehensive Research Network.

13.8. Indemnity

This is a clinician-initiated study. The Sponsor (University of Birmingham) holds Public Liability (negligent harm) and Clinical Trial (negligent harm) insurance policies, which apply to this trial. Participants may be able to claim compensation, if they can prove that the University of Birmingham has been negligent. However, as this clinical trial is being carried out in a hospital setting, NHS Trust and Non-Trust Hospitals have a duty of care to the patients being treated. Compensation is only available *via* NHS indemnity in the event of clinical negligence being proven. University of Birmingham does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove

negligence on the part of University of Birmingham or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the CI, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office. There are no specific arrangements for compensation made in respect of any SAE occurring though participation in the trial, whether from the side effects listed, or others yet unforeseen.

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

14. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

14.1. AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the grant holders. On completion of the study, the study data will be analysed and tabulated, and a final study reported prepared for the NIHR. A writing committee may be established to prepare the report and any subsequent papers.

The main report of the trial will be published in the name of the C-STICH Collaborative Group, acknowledging the writing group as authors. Subsequent publications should also be published in the C-STICH Collaborative Group name, but those academics who contribute to specific aspects may be listed as authors.

14.2. PUBLICATION

A meeting will be held after the end of the study to allow discussion of the main results among the collaborators prior to publication. The success of the study depends entirely on the wholehearted collaboration of a large number of doctors, nurses and others. For this reason, chief credit for the main results will be given not to the committees or central organisers but to all those who have collaborated in the study. Centres will be permitted to publish data obtained from participants in the C-STICH Trial that use Trial outcome measures but do not relate to the trial randomised evaluation and hypothesis.

14.3. Ancillary studies

It is requested that any proposals for formal additional studies of the effects of the trial treatments on some patients (e.g. special investigations in selected hospitals) be referred to the Trial Management Committee for consideration. In general, it would be preferable for the trial to be kept as simple as possible, and add-on studies will need to be fully justified.

15. REFERENCES

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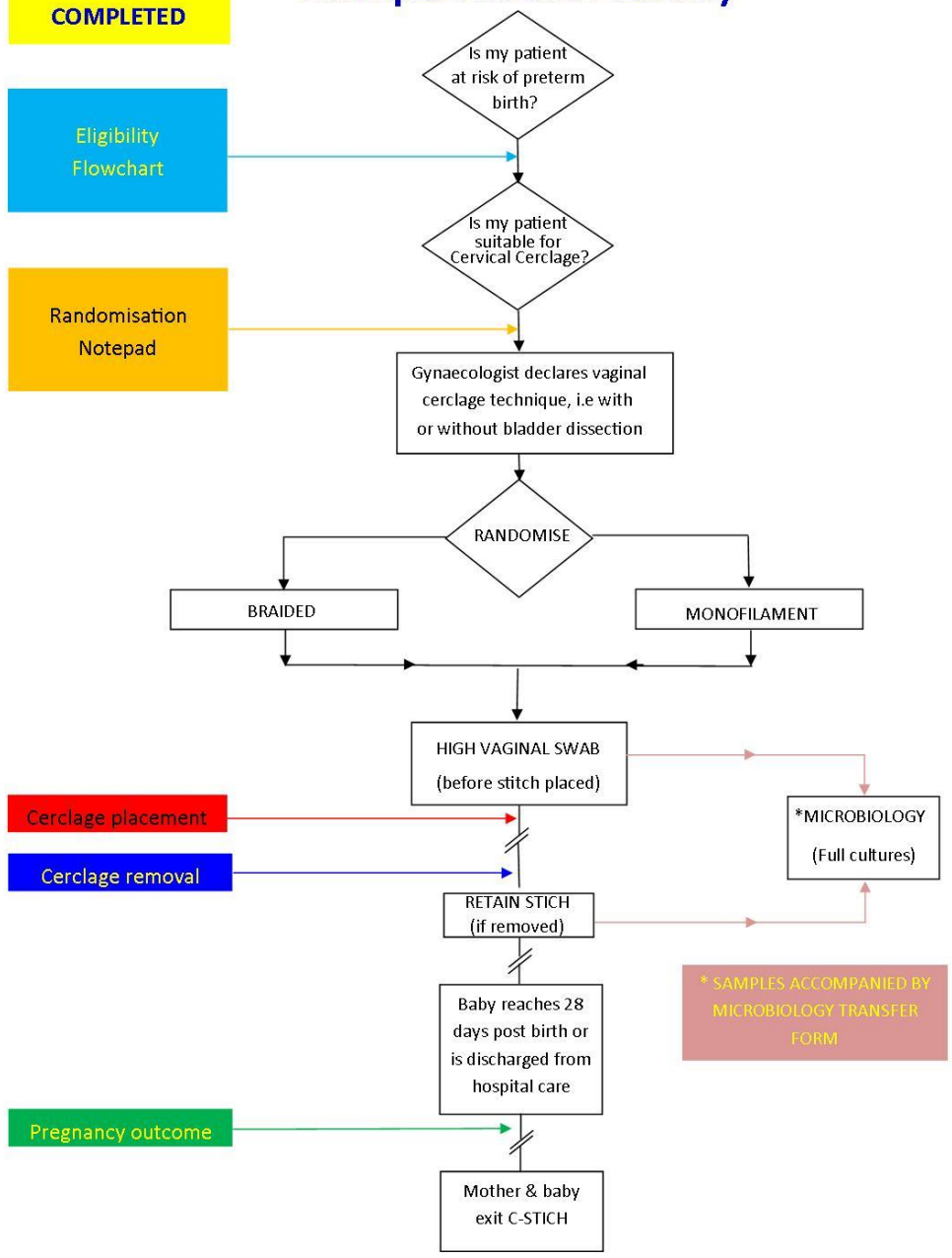
C-STICH TRIAL SCHEMA

The Cerclage Suture Type for an Insufficient Cervix and its effect on Health outcomes Trial: a randomised controlled Trial of monofilament versus braided sutures for insufficient cervix

C-STICH NOTEPAD COMPLETED

Example Patient Pathway



C-STICH ELIGIBILTY FLOWCHART

The Cerclage Suture Type for an Insufficient Cervix and its effect on Health outcomes Trial: a randomised controlled Trial of monofilament versus braided sutures for insufficient cervix

Is my patient suitable for C-STICH?

The flowchart below will quickly let you know if your patient is eligible for the C-STICH trial.