Cerclage outcome by the type of suture material (COTS) study: randomised pilot/feasibility study comparing monofilament (intervention) sutures versus multifilament (comparison) for cervical cerclage.

By

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Synopsis

This research work provided the necessary information for planning a definitive trial investigating the clinical effectiveness of monofilament non-braided suture materials in reducing pregnancy loss rate following cervical cerclage compared to the traditional multifilament braided sutures.

The main aim of COTS was to conduct a feasibility / pilot RCT to study a number of aspects of how the main trial will be optimally delivered.

COTS provided necessary information to plan and confidently run a definitive trial that will be able to determine the clinical and cost effectiveness of the different types of suture material. If the current perceived benefit of monofilament sutures is confirmed, this policy will be rapidly adopted nationally. In the UK alone this could potentially prevent more than 300 babies per annum dying as a result of mid-trimester loss, intrauterine infection or complications of prematurity. Moreover, reducing the risk of prematurity will reduce neonatal unit and hospital stay, the significant morbidity associated with early gestation and the associated long-term morbidity. This will have psychosocial benefits and significant cost saving for the NHS and the wider community.

- I have conducted a retrospective analysis of a cohort of pregnant women who had history indicated or ultrasound indicated cervical cerclage using either Nylon (monofilament unbraided) suture or Mersilene (braided) suture at Birmingham Women's Hospital and Addenbrookes Hospital in Cambridge from January 2004 till

December 2010. The data collection was later extended to March 2015 and combined with retrospective data from King's College London Professor P Bennet's group and published. Data was collected and analysed within the frames of audit recommended by RCOG looking at the pregnancy loss rate at less than 24 weeks of gestation and preterm delivery at 24-32 weeks of gestation in each unit.

- I have conducted a national survey of Consultant Obstetricians and Gynaecologists based in the UK to identify the type of suture materials commonly used for cerclage. I have reviewed current practice with regards to criteria used for recommending cerclage; explored their willingness to participate in pilot/feasibility study and ensured the relevance of selected outcomes for the RCT.

- I have performed a systematic review of the published literature on Medline, CINAHL and Embase. My objective was to evaluate rate of pregnancy loss associated with the type of suture material used for history indicated and ultrasound indicated cervical cerclage comparing braided (multifilament) versus non-braided (monofilament) sutures.

- After this preliminary work I have developed trial documents. I have tested the study protocol that has been designed with the full scale trial in mind. I have developed and established an active COTS-PPI group that had an active role at the outset of the feasibility project and participated throughout the definitive trial. I have gained insight into any professional or organisational barriers that were obstacles to a full study. I have tested recruitment and randomisation procedures. I have calculated an accurate

estimate of NHS and service costs involved as well as the level of resource required to ensure successful delivery of the full trial. I have examined general data collection, cleaning, input and analysis procedures, and established the benefits of the one type of suture over the other in cases of elective cervical cerclage.

The size of the *pilot study* did not allow reliable assessment of the effect of the different suture materials on clinical outcomes. However, we did collect information from collaborating units on the numbers of women requiring cervical cerclage and eligible for the study and those women's birth outcomes. This gave a larger prospective sample on which to base the power calculation. COTS enabled me to precisely estimate (a) the recruitment rate, (b) attrition rate, and (c) rate of occurrence of the primary outcome in both groups. During the pilot study, accurate assessment of the numbers of women eligible, approached and recruited was made.

Based on the findings of COTS trial, funding was sought from the NIHR HTA programme, and we were successful in being awarded £1.2 million (co-applicant) to conduct a multi-centre randomised controlled trial (RCT): The C-STICH trial 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.

DEDICATION

I dedicate my thesis to my grandmother Professor Solmaz Israfil-Bayli whose love and dedication to the field of obstetrics and gynaecology made me choose this specialty. I dedicate this work to my parents Nigar and Philip Maxwell and my sons Emin and Maxud whose unconditional love and support enabled me to be where I am today.

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At the end I would like to thank Mrs Yvonne Gateley who made me think that I can accomplish this work and be happier.

Publications from this thesis

- Use of different suture material multifilament braided sutures versus monofilament non-braided sutures in planned (elective) cervical cerclage: Systematic review and meta-analysis. **Israfil-Bayli F**, Harb H, Toozs-Hobson P- awaiting submission for publication
- Relationship between vaginal microbial dysbiosis, inflammation, and pregnancy outcomes in cervical cerclage. Kindinger LM, MacIntyre DA, Lee YS, Marchesi JR, Smith A, McDonald JA, Terzidou V, Cook JR, Lees C, **Israfil-Bayli** F, Faiza Y, Toozs-Hobson P, Slack M, Cacciatore S, Holmes E, Nicholson JK, Teoh TG, Bennett PR. Sci Transl Med. 2016 Aug 3;8(350)
- Cerclage outcome by the type of suture material (COTS): study protocol for a pilot and feasibility randomised controlled trial. **Israfil-Bayli** F, Toozs-Hobson P, Lees C, Slack M, Ismail K. Trials. 2014 Oct 27; 15:415
- Cervical cerclage and type of suture material: a survey of UK consultants' practice. **Israfil-Bayli** F, Toozs-Hobson P, Lees C, Slack M, Daniels J, Vince A, Ismail KM. J Matern Fetal Neonatal Med. 2014 Oct;27(15):1584-8
- Pregnancy outcome after elective cervical cerclage in relation to type of suture material used. **Israfil-Bayli** F, Toozs-Hobson P, Lees C, Slack M, Ismail KM. Med Hypotheses. 2013 Jul;81(1):119-21

Presentations from this thesis

- Birmingham and the Black Country Comprehensive Local Research Network, Reproductive Health and Childbirth Group (REACH) Priority Meeting on 1st February 2012, Birmingham, UK (Invited speaker)
- Maternal Medicine and Preterm Birth Clinical Specialty Group held at British Maternal and Fetal medicine Society (BMFMS) on 20th April 2012, Glasgow, Scotland (Invited speaker)
- Surgery Research Writing Workshop, NIHR organised event, April 2012 (Participant)
- BMOGS (Birmingham and Midland Obstetrical and Gynaecological Society) meeting, May 2013 (Keynote speaker)
- Annual Academic Meeting and Blair Bell Society Meeting, poster presentation, 2013, RCOG, London, UK
- PRIME (Public and Researches Involvement in Maternity and Early pregnancy) meeting, University of Birmingham, 30th January 2013, Birmingham, UK (Invited speaker)

Contents

ABBREVIATIONS

BCTU	Birmingham Clinical Trials Unit
BSUG	British Society of Urogynaecologists
COTS	Cerclage Outcome by the Type of Suture material
FDA	Food and Drug Administration
HTA	Health Technology Assessment
LLETZ	Loop Electrical Excision Procedure
MHRA	Medicines and Healthcare Products Regulatory Agency
MOS	Monofilament Suture
MRC	Medical Research Council
MUS	Multifilament Suture
NHS	National Health Service
NIHR	National Institute for Health Research
NICE	National Institute of Clinical Excellence
NRS	Non-randomised studies
POP	Pelvic Organ Prolapse
PPROM	Preterm Prelabour Rupture of Membranes
PTB	Preterm Birth
RCOG	Royal College of Obstetricians and Gynaecologists

RCT	Randomised Controlled Trial
SCJ	Squamocolumnar junction
SMTL	Spontaneous Midtrimester Loss
SUI	Stress Urinary Incontinence
TA	Transabdominal scan
TVS	Transvaginal scan
TVT	Tension free Vaginal Tape
UK	United Kingdom
US	United States of America
WHO	World Health Organisation

Chapter 1 – Literature Review

1.1 Preterm birth

1.1.1 Definition and incidence

Preterm birth is defined as birth before thirty-seven completed weeks of pregnancy (less than 259 days after the last menstrual period). It is subdivided according to gestational age into following categories: extremely preterm (<28 wk), very preterm (28–31 wk) and late preterm (32–36 wk). Preterm birth remains one of the main challenges for modern obstetrics and maternity care worldwide and is World Health Organisation priority[1]. Despite recent advances in perinatal care, premature delivery remains the main cause of perinatal mortality and morbidity in developed countries. Globally with the incidence of 28% PTB constitutes the main direct cause of neonatal death worldwide, surpassing severe infections (26%) and asphyxia (23%)[2]. PTB remains the second most common cause of death even in children up to 5 years of age. The current incidence of preterm birth in high income countries is 9 % and it is still rising in some countries. According to the data from the report, by Liu L et al[3] 1.1 million babies die each year in the world as a result of prematurity and many of those who survive remain disabled. The World Health Association (WHO) undertook a review of preterm birth incidence rate worldwide with all UN member states participating. The review estimated that fifteen million babies were born prematurely in 2010 with 5% born severely premature (defined as under 28 weeks of gestation). In UK approximately 60,000 babies are born prematurely every year with around 10,000 babies being born at a gestation of <32 weeks. Tragically, approximately 1,500 of them die. Gestational age at delivery is inversely proportional to mortality, so that the earlier the gestation at delivery the higher the mortality and requirement for intensive care admission. There is also a greater risk of disability and the need for additional support in those that survive with life-long disabilities. Recently it has been acknowledged that the gestational age rather than birth weight predominantly

determines the outcome- survival and long-term consequences of birth[4]. For example, currently babies born at 32 weeks of gestation have perinatal mortality of 2% but it reaches 90% for those born at 23 weeks[5]. In circumstances where the gestational age where the gestational age is not known birth weight can be as used as a surrogate for example: <1,000 g for extremely preterm birth (<28 wk) and 1,000 to <1,500 g for very preterm birth (28–31 wk).

1.1.2 Neonatal complications

Children born prematurely quite often develop additional complications/morbidities for example underdeveloped lungs, leading to respiratory distress syndrome, which requires ventilation support and admission to neonatal unit, bronchopulmonary dysplasia, intraventricular haemorrhage, retrolental fibroplasias and retinopathy of prematurity (ROP). They also may have developmental problems, learning difficulties and behavioural problems in later life. Further sequelae are that premature children are more prone to development of chronic lung and heart conditions, attention deficit disorder, asthma, diabetes and hypertension in later life. Diabetes and hypertension in mothers are associated with increased risk of preterm birth, so prenatal and antenatal care for women affected by those conditions is of paramount importance as preterm babies themselves have a significant chance of developing chronic conditions such as hypertension and diabetes in later life "creating an intergenerational cycle of risk"[6], meaning that events in one generation may have far reaching consequences into subsequent generations.

1.1.3 Financial implications

There is a correlation between gestation at delivery and likelihood of admission to a neonatal unit and/or a need for special support which can last for many weeks and sometimes

months. It is estimated that 10% of healthcare resources in developed countries is spent on dealing with these consequences. In the UK the cost of preterm birth and its complications imposes a significant health care cost burden on NHS where the annual cost to the NHS for neonatal care is approximately £2.9billion[7].

1.1.4 Emotional implications

Apart from a colossal economic impact on health care resources, preterm birth and its consequences has a potential to have significant negative impact of family, parents and bonding[8]. Parental stress can be very high when children are born prematurely. A recent meta-analysis confirmed that child-related stress is evident more in parents of preterm babies when compared to with full term ones[9]. Deater-Deckard K defined parental stress as "a mismatch between perceived resources, expectations and actual caregiving demands"[10]. There is some evidence that the levels of this stress has decreased over the years as a result of advances in health care systems and its implications on the outcome of children born prematurely[9]. The Parenting Stress Index-Full Form PSI-FF was developed to grade such stress. A premature birth may also influence parental attachment bonds, which are considered an important part of parental behavior which leads to the development of caregiving in the future. This quality is significantly diminished in parents of preterm babies. In order to enhance the ability of a preterm born child's parents to cope with stress, several interventions have been developed. The fundamental principles of any intervention are psychological support, parent education and certain developmental therapeutic programs for children[11]. According to the recent RCT the early intervention, for example implementation of Mother-Infant Transaction Program (MITP), decreases stress among parents of prematurely born children and improves bonds between parents[12].

1.1.5 Causes of preterm birth

(Chang HH et al) recently looked at the data from thirty-nine countries with very high human development index (VHHDI) in order to understand trends in preterm birth, its causes and evidence-based intervention to reduce its incidence[13]. USA remained one of the countries with the highest preterm birth rate with non-medically induced labour, assisted reproduction and increased rate of caesarean section being significant factors. In order to decrease the incidence of preterm birth several interventions could be implemented pre-conceptually, throughout the pregnancy and labour. These interventions could potentially lead to a relative 5% reduction in preterm birth rate (from 9.59% to 9.07%) in the thirty-nine countries with the VHHDI. The 'Born Too Soon Report' published in 2012 sets the goal of 50% decrease in a rate of preterm birth related mortality by year 2025. Five interventions were identified in this report:

1. Reduction in elective C-sections and inductions of labor without an absolute indication
2. Reduction in multiple embryo transfers during fertility treatment
3. Smoking cessation programmes for pregnant women
4. Provision of high- risk pregnant women with progesterone supplementation
5. Performing cervical cerclage procedure on women with short cervixes

These interventions were estimated to affect a reduction in 58 000 preterm births in the USA and save three million US dollars annually[13].

The risk of preterm birth is also affected by pre-conception advice, medical and surgical interventions. Pre-conception identification of risk factors and early counselling gives a chance for the implementation of behavioural changes such as smoking cessation and

optimisation of chronic medical conditions such as diabetes and hypertension. It is always important to consider prolongation of only healthy pregnancy and assess influence on perinatal mortality/morbidity[5]. This is because in some cases, preterm birth is a tool for nature to stop the pregnancy as its prolongation may harm the fetus staying in an adverse intrauterine environment. Prolongation of such pregnancies may cause harm to the fetus and lead to neonatal mortality and morbidity rather than benefit.

There are preconception surgical interventions such as correcting structural abnormalities that can reduce the risk of preterm birth. Such procedures are aimed at normalising uterine anatomy where it is deficient, but evidence is limited. Other examples, such as pre-conceptional placement of abdominal cerclage whether laparoscopically or transabdominally have been tried. Again there is no reliable data. The MAVRIC (Multicentre randomized trial of high versus low versus abdominal cerclage in women with a previous failed stitch) at the time of writing this thesis trial is still ongoing but they have problems with recruitment. Nevertheless, vaginal cervical cerclage is included into interventions aimed to reduce rates of preterm birth specified in the “Born Too Soon Report” and occupies third place after smoking reduction and decreasing multiple embryo transfers during assisted reproductive technologies. Cervical cerclage is currently offered to women with a history of SPTL or MTL between 16+0 and 34+0 weeks of a previous pregnancy and in whom a transvaginal ultrasound scan has been carried out between 16+0 and 24+0 weeks of pregnancy that reveals a cervical length of less than 25mm[14]. Cervix may shorten and dilate afterwards due to cervical insufficiency or incompetence. The next section describes anatomy, histology and physiology of cervix to explain the concept of cervical incompetence.

1.1 Cervix

1.2.1 Anatomy

The cervix represents the lower inferior third of the non-pregnant normal sized uterus [15]. In adult non-pregnant females, the cervix is cylindrical in shape 2.5-3.0 cm long and 2-2.5 cm in diameter. After pregnancy and childbirth it becomes more barrel shaped [16]. The ratio of the uterine body to cervix changes throughout life. The body to cervix ratio is 2:1 in adult non-pregnant females, the same as at the birth of a female fetus when the uterus is quite large and is mainly an abdominal organ because of the intrauterine influence of maternal hormones. In childhood the cervix is the same length as the body so the ratio is 1:1. After the menopause when a uterine body atrophies in size significantly the same proportion with the cervix is achieved.

The junction between the cervix and the main body of the uterus is a zone called the isthmus of the uterus, which is approximately 1 cm long. The cervix itself is divided into the supravaginal part, which lies between the isthmus and the vagina and the vaginal portion below, which is situated at the top of the vagina. The supravaginal portion in the abdomen lies between the bladder and the rectum. It is separated from the bladder anteriorly by connective tissue[15]. There is a space between the supravaginal portion of the cervix and the rectum called the Pouch of Douglas or recto-uterine pouch.

The cervix contains a central canal, which connects the uterine cavity to the vagina. The canal is fusiform in shape. It extends from the narrowed part inside the isthmus, (the anatomical internal os), down through the supravaginal part and vaginal part of the cervix into the vagina through the external os[15]. The external os is different in shape in parous and nulliparous women. In parous women the external os looks like a transverse slit, which

divides the cervix into anterior and posterior lips. In nulliparous women the external os is circular. The cervical canal, together with the uterine cavity and the vagina, forms a birth canal through which a fetus passes down during labour.

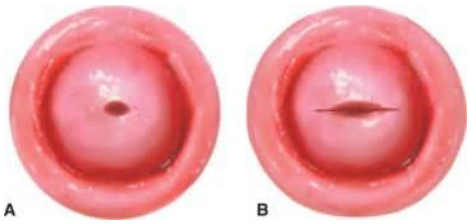


Figure 1. Cervix in nulliparous and parous women

The uterus and ovaries are supported by several ligaments. The two main ligaments attached to the cervix are called the uterosacral and cardinal ligaments. The cardinal ligaments, which are also called transverse cervical ligaments, extend from the supravaginal part of the cervix to the lateral pelvic side wall. The ureters run in the transition between the cardinal and broad ligaments inferior to the uterine arteries, 2 cm lateral to the supravaginal part of the cervix. The uterosacral ligaments extend from the superior posterior aspect of the cervix to the middle of the sacrum. Their division and suturing during hysterectomy plays an important role in the prevention of subsequent vault prolapse [17].

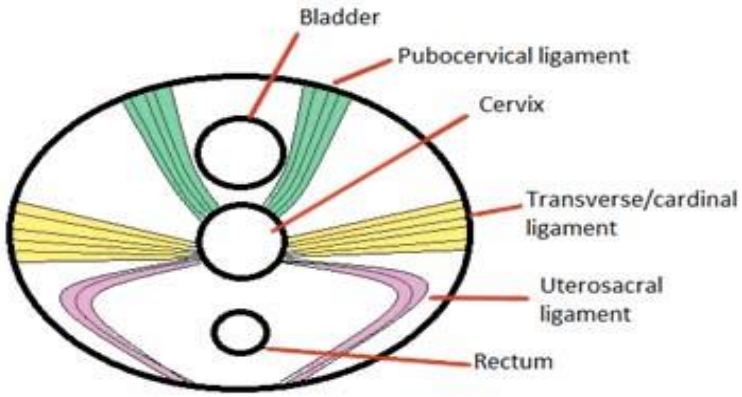


Figure 2. Ligament support to the cervix

The blood supply to the cervix is derived from branches of the uterine artery. The uterine veins drain the blood from the cervix as well as the uterus and runs within the broad ligament, forming a venous plexus on each side of the cervix. The veins run parallel to the arteries.

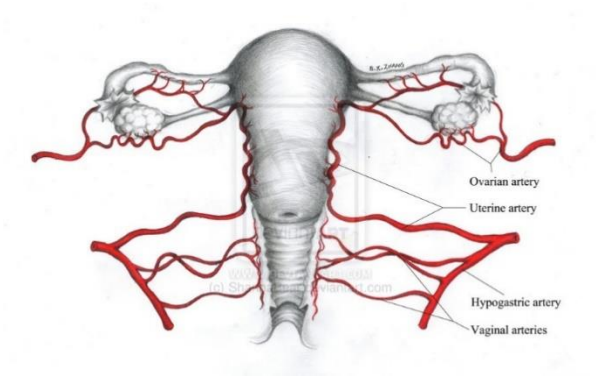


Figure 3. Blood supply to the cervix

The nerves to the cervix derive from the uterovaginal nerve plexus. This plexus is situated at the junction of the base of the broad ligament and the superior part of the transverse cervical ligament. It represents one of the pelvic nerve plexuses derived from the hypogastric plexus. It contains sympathetic, parasympathetic and afferent visceral fibres. Sympathetic fibres originate from the inferior thoracic spinal cord segments, they pass through lumbar splanchnic nerves and intermesenteric-hypogastric-pelvic plexuses. The parasympathetic nerves come from the S2-S4 spinal cord segments and go through the pelvic splachnic nerves to the inferior hypogastric-uterovaginal plexus. The visceral afferent innervation is divided into superior and inferior components. The inferior one or subperitoneal passes impulses from the subperitonel part of the cervix and vagina. The afferent fibres go parallel to parasympathetic fibres through uterovaginal and inferior hypogastric plexuses, pelvic splanchnic nerves. Those nerves reach spinal sensory ganglia of S2-S4[15].

Lymphatic vessels run alongside the blood vessels that supply the uterus and along ligaments supporting it. Lymphatic vessels from the cervix run along uterine blood vessels, within the cardinal ligaments to internal iliac lymph nodes. They also run alongside uterosacral ligaments to the sacral lymph nodes.

1.2.2 Histology

The cervix varies significantly histologically from the rest of the uterus. The non-pregnant cervix is a fibrous structure as opposed to the uterus, which is comprised mainly of smooth muscle- myometrium. It is mainly composed of collagen with only a small portion of smooth muscle and elastin[15]. Smooth muscle fibres are embedded into collagen. The proportion of muscle to collagen changes through a woman's life and is affected by parity.

The vaginal part of the cervix is called ectocervix. It is covered with non-keratinised stratified squamous epithelium which continues into the vagina. It is rich in glycogen in females of reproductive age and undergoes cyclical changes under the influence of female sex hormones. The concentration of glycogen in the cells is less before the menarche and after the menopause when the epithelium is much thinner and has fewer layers[18]. The lining of the cervical canal is called the endocervix. It consists of a single layer of columnar mucus-secreting epithelium- endocervical epithelium[18]. The 3-dimensional studies indicate that there are numerous invaginations of the mucus-secreting epithelium extending into cervical stroma[18]. This arrangement greatly increases the surface for mucus production.

The border or junction between the squamous epithelium of the ectocervix and the mucous secreting columnar epithelium of the endocervix is called the squamocolumnar junction (SCJ), which usually lies close to the external os. Under the influence of sex hormones, principally oestrogen, at puberty the cells of the columnar epithelium proliferate resulting in the SCJ moving the endocervical cells into the vagina, forming an ectropion. Concurrently during puberty the pH of the vagina changes and becomes acidic (pH 3)[18]. The exposure of the sensitive columnar epithelium of the ectropion to the acidic environment induces squamous metaplasia and creates a transformation zone where the ectocervical columnar

epithelium change towards squamous epithelium[18]. The transformation zone is composed of new cells of pseudosquamous epithelium.

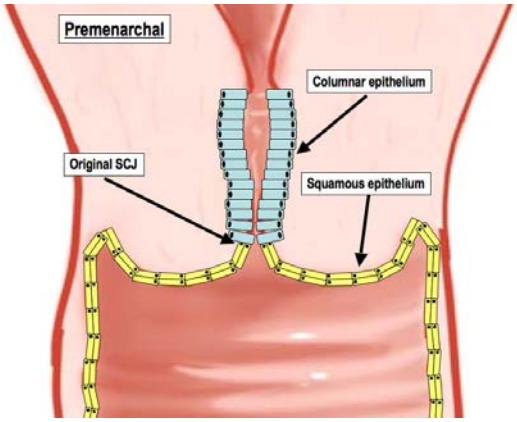


Figure 4. Squamocolumnar junction

Constant changes in the epithelium may sometimes lead to the formation of abnormal cells and intraepithelial neoplasia[18]. When the endocervical mucous glands get obliterated or blocked then the mucin which they produce cannot be secreted into the vagina. It accumulates within the glands and presents as flat surfaced lesions on the cervix called Nabothian follicles or cysts. Under normal circumstances cervical mucous produced by endocervical glands is excreted directly into the endocervical canal and thereafter into the vagina. Cervical mucus inside the cervical canal undergoes different changes under the influence of progesterone through the menstrual cycle. This mucous plays an important part in the process of fertilisation and early pregnancy. The consistency of the mucous changes through the cycle: 1) at ovulation mucous is very watery which helps for the passage of sperm to the uterine cavity. 2) luteal phase – the mucous is very thick and hinders the passage of sperm[16]. The excretion of the mucous into the vagina is facilitated by a small number of ciliated columnar epithelial cells placed among mucus-secreting endocervical cells[18]. This passage of mucus into the vagina contributes to vaginal lubrication during intercourse.

During pregnancy the cervix becomes very rigid[16], in order to keep the pregnancy inside the uterus, but just before delivery the process of cervical effacement takes place during which connective tissue in the cervix undergoes significant changes. The concentration of hyaluronic acid in the glycosaminoglycan matrix between the collagen fibres increases

significantly. It attracts water and as a result, separates collagen fibres from cervical stroma and makes the cervix very soft. Usually collagen and elastin fibres are held together by dermatan sulphate bridges. During pregnancy concentration of this compound decreases significantly and, as a result, those bridges are weakened which leads to separation of the fibres and further softening of the cervix[18]. The collagen fibres themselves (type I and type II) separate from each other and become short. They also lose their parallel alignment and become more haphazard, as a result the cervix softens and - loses its resistance[18]. If this process happens earlier in pregnancy pregnant women may suffer a miscarriage or premature labour.

There are certain changes within the endocervical canal during pregnancy which are especially important in the context of this research work. As previously mentioned, the endocervical canal contains mucus which changes its consistency throughout the menstrual cycle. Mucin inside this mucous acts as an antibacterial substance and prevents the spread of bacteria from the vagina into uterine cavity[18]. At the beginning of pregnancy, the mucous inside the canal becomes very thick and forms a mucous plug which remains there until the end of the third trimester preventing ascending infection. The challenge is to identify and/or to modify the trigger to this process to prevent or delay preterm labour/second trimester miscarriage. Whether changes to the cervix lead to the mucus plug being lost and the consecutive delivery of the fetus prematurely; or changes in the mucous plug which loses its antibacterial qualities, followed by infection which leads to premature birth/miscarriage has yet to be fully understood.

1.3 Cervical incompetence

Cervical incompetence or insufficiency can be defined as the inability of the uterus to keep pregnancy until full term due to a structural or functional problem[19]. It occurs in 1% of all pregnancies and has a recurrence rate of almost 30%[19].

As such approximately 2,000,000 cerclage procedures are performed worldwide annually. The majority of those procedures are planned and performed vaginally. Based on our survey, 0.5% of pregnant women booked in surveyed units had elective or ultrasound indicated cerclage. As a result, approximately 6700 pregnant women are diagnosed with an insufficient cervix in the UK each year. So far there is no evidence to support or completely reject the use of cervical cerclage. Several RCTs combined in meta-analysis failed to demonstrate any evidence to support the use of cerclage[20, 21]. The recent Cochrane review concluded that the procedure reduces the incidence of early delivery in patients at risk of recurrent preterm birth but has no statistically significant impact on perinatal mortality or morbidity[22].

First time cervical insufficiency or cervical incompetence was mentioned in literature as far back as 1658 by Riverius[23]. He described it as a condition when “the orifice of the womb [being] so slack that it cannot rightly contract itself to keep in the seed”. Three centuries later, the fathers of cervical cerclage Dr Shirodkar and Dr McDonald described the condition as a history of painless cervical dilatation which led to second trimester miscarriage or preterm birth in the absence of any other causative factors[24]. The diagnosis of cervical insufficiency has evolved over time. It is quite often made retrospectively once all other causes for MTL and preterm birth are excluded. Today diagnosis is made based on cervical length measurements that are determined by transvaginal ultrasound scan. The predictive

value of those measurements depends on women's risk status. Irrespective of the women's status the shorter the length of the cervix the higher is the risk. But in low risk women with cervical length less than 25 mm the risk of preterm birth remains half of the risk of preterm birth in women who are identified as high risk group[25].

Vaginal ultrasound assessment of the cervix is offered to women with history of previous preterm births or MTLs before 24 weeks gestation the current pregnancy.

Term incompetence is deemed to have a connotation with failure for patients and has now become largely obsolete.

1.3.1 Causes

Some authors have attempted to classify cervical insufficiency depending on possible causative factors[26]. Acquired incompetence may be due to previous obstetrical or gynaecological procedures that distort cervical anatomy or cause trauma to the cervix. Rarely cervical weakness can be due to congenital causes leading again to anatomical or sometimes histological defect. Cervical anatomy can also be distorted by the presence of intramural pathology such as low-lying myomas or fibromas.

The most important anatomical part of the cervix essential for normal cervical functioning is the internal os. Both ultrasound and MRI imaging studies prove and confirm that cervical shortening begins at internal os where cervix starts to dilate leading to funnelling[27] of the cervix. A second, not so well reported, method of cervical assessment is elastogarphy. It provides information about cervical consistency especially internal os. It presents the ability of tissue to deform under pressure. Obviously the softer the tissue, the easier it changes its shape. There are different types of elastography: firstly, static when tissue displacement in response to manual compression or physiological movements of vessels is measured, or

dynamic, when the speed of shear wave propagation is determined. Elastography provides information on the internal os stiffness; this parameter, impossible for manual assessment, was shown to correlate with pregnancy outcome and is a strong predictor of preterm delivery[28].

The stiffness is determined by the means of strain elastography, using colour scale. There are few studies that demonstrated an association between elasticity of internal os and the risk of preterm birth. Women with soft internal os (yellow or red colour on scale) on assessment by elastography were identified of being at higher risk of preterm birth[29, 30].

One of the main recognised iatrogenic causes of cervical insufficiency is previous excisional treatment to the cervix (cone biopsy or loop electrical excision of the transformation zone (LLETZ) procedure) for cervical intraepithelial neoplasia. Excision of the external part of the cervix makes the cervix shorter and puts women at risk of preterm birth (PTB)[31]. The link is stronger with more aggressive treatment, such as knife cone and with bigger volume of tissue removed during the procedure. Expressly the correlation between PTB and cone biopsy is more pronounced when the length of cervix excised is more than 20 mm. Quite interesting that there is also some evidence from a cohort of women with untreated CIN that there remains a high rate of preterm birth. This suggests that presence of CIN can lead to certain changes in the cervix that subsequently lead to preterm birth even without the treatment[32]. The mechanism is still not fully understood. One hypothesis suggests that immunological or biochemical changes in cervix leading to altered process of parturition[33], However it remains more likely that it is the anatomical destruction of cervical tissue which is critical to the risk of PTL[34].

A second factor is the impact of HPV infection and preterm birth. Zhuang et al [35]demonstrated that rate of preterm birth increased in cohort of women with high risk HPV. HPV infection in itself does not cause chorioamnionitis in the way seen in most bacterial infections, inferring that it leads to preterm delivery via a different route.

Biochemical changes affecting cervical extracellular matrix (ECM) play a key role in adequate mechanical function of the cervix[36]. The ECM is mainly composed of Type I and III collagen, which play a major role in mechanical support for the cervix. As mentioned earlier, in this chapter there are also a significant number of proteoglycans in cervix, which are important for organisation of collagen fibres. Change in the ECM composition leads to cervical shortening and softening which in turn leads to preterm birth. Additional invasion of leucocytes and proteolytic enzymes lead to cervical remodelling[37]. Again the exact mechanism remains unknown. It is also reported that the levels of inflammatory cytokines such as IL-6, MMP- are increased 8 in women with short cervix.

1.3.2 Diagnosis

There are no objective investigations or tests that can be performed before pregnancy to predict or diagnose subsequent cervical insufficiency. Diagnosis historically has almost always been clinical and retrospective depending on history and exclusion of other causes of the preterm birth. Hysterosalpingography and use of cervical dilators have been used in the past as diagnostic procedures prior to pregnancy but are no longer[38]used. Cervical weakness affects 1% of pregnancies hence, it occurs in approximately 2,000,000 pregnancies globally per annum[39]. If a woman had a history of second trimester miscarriage(s) or early preterm birth which was accompanied by spontaneous rupture of membranes or painless cervical dilatation prior to it with no other cause known, then

diagnosis of cervical insufficiency is made. Later in pregnancy a speculum examination can be performed to confirm the presence of cervical dilation and fetal membranes in the vagina, in which case emergency cerclage can be offered. Since the mid 1990s, transvaginal scan (TVS) has increasingly been used to predict the condition based on the scan of cervical shortening detected between 14 and 24 weeks of gestation.

The advantage of ultrasonographic assessment of the cervix that it is more accurate than clinical examination for prediction of PTB. It is not associated with any complications and is acceptable by 99% of patients only 2 % reporting discomfort/pain[40]. It can be done transvaginally, transabdominally and through transperineal and translabial approach. It has been proven in several studies that sonographically short cervix in midtrimester is associated with an increased risk of spontaneous preterm birth in singleton and multiple pregnancies irrespective of history of PTB in the past[41]. Romero et al concluded that the CL was sensitive with the cervical length being inversely correlated with the risk of spontaneous PTB. However, 75% of women with short cervices do not deliver preterm and therefore it was not specific. So the accuracy of cervical length measurement as a predicting tool for PTB is only valid in a high risk population[42]. Other authors looked into correlation between shortened cervical length and timing of preterm birth[43]. They have noted that women with a shortened cervical length were more likely to deliver within 4 weeks of their cervical length evaluation than women with longer cervical lengths. Currently transvaginal ultrasound examination of the cervix is widely recommended to identify women at high risk of preterm delivery. Use of cervical length measurements in low risk population is still quite debatable[44]. The sensitivity of CL measurement in this cohort is about 30-40% as may be PTB in those women is not related to the abnormal CL. The 2013 Cochrane review for Cervical Assessment by Ultrasound for Preventing Preterm Delivery concluded that CL measurement

by TVS is one of the best predictors of PTB in all populations but there is insufficient evidence to recommend routine screening of asymptomatic or symptomatic pregnant women with TVS without any intervention[45].

Currently a cervical length 'cut off' of 25 mm (10 th centile) has been chosen in clinical practice or sometimes 15 mm (the second percentile). The cervix measuring less than 25 mm is called short [42]and may be indicative of preterm birth[46]. The normal cervical length is between 15 -50 mm. Timing of a scan and relation to gestational age is important and detection of short CL is directly linked to probability of PTB. For example, CL at of 20 mm at 16 weeks is associated with higher incidence of PTB than the same CL detected first at 20 or 24 weeks[47]. Measurements before 14 weeks of gestation are not very helpful as women who will deliver extremely preterm usually have CL 25 mm in the first trimester.

Cervical insufficiency cannot be considered a simple dichotomous diagnosis, as it is a risk which is influenced by several factors such as the anatomy of the cervix and other factors leading to the process of cervical premature dilatation[48].

1.3.3 Treatment

Cervical cerclage, vaginal and intramuscular progesterone, a cervical pessary, or a combination of cervical pessary and vaginal progesterone have all been tried as treatments for cervical insufficiency.

Cervical pessary showed promise in a series of non-randomised studies. These were followed by a Cochrane[49] review, which concluded that the evidence was not robust or statistically significant and suggested the need for a full randomised control trial. Two large randomised trials have subsequently been published with contradicting evidence[50, 51].

Both trials aimed to lower the rate of spontaneous birth before 34 weeks of gestation in women with singleton pregnancies and short cervix on a transvaginal scan compared with expectant management. A silicone pessary was placed around the cervix to support it and reduce pressure from the pregnancy on the cervical canal. Initial data from the PECEP (The PEsario Cervical para Evitar Prematuridad) trial had 192 women who had a short cervix on an ultrasound scan had a cervical pessary inserted and 193 had expectant management. The spontaneous birth rate was significantly lower in the pessary group (6% versus 27%, odds ratio 0.18, 95% CI 0.08-0.37; p<0.0001). The rate of the preterm birth before 28 weeks and 37 weeks of gestation was also reduced and gave hope for this simple method of prevention of preterm birth[50]. However, the latest trial by Nicolaides and his group has shown that there was no significant difference in the rate of spontaneous birth before 34 weeks of gestation between pessary and control group. (12.0% and 10.8%, respectively; odds ratio in the pessary group, 1.12; 95% confidence interval, 0.75–1.69; P = 0.57). Importantly there was also no difference in neonatal outcomes[51].

Forty-five percent of participants in the later trial had a CL < 15 mm on TVS were also treated with vaginal progesterone. The PECEP trial didn't report use of progesterone. Goya et al also reported substantially higher rate of PTB among controls than Nicolaides et al, which remained unexplained. Patients enrolled into Nicolaides trial were at least as likely as those in the PECEP trial to have major risk factors for preterm delivery, including previous PTB and very short cervix. The potential reason for the lack of demonstrable effect of the pessary is that any reduction in PTB may have been achieved by progesterone and so that there is no added benefit of pessary.

The second method of preterm birth/second trimester miscarriage prevention is use of progesterone, which promotes myometrial quiescence and inhibits cervical ripening by down

regulating the production of cytokines. The premature cervical shortening is proposed to occur because of progesterone blockade which leads to loss of mucosal plug in cervical canal allowing bacteria to set up an inflammatory process around the fetal membranes.

Progesterone use has been evaluated in different studies. The most common forms to be used an intramuscular 17-hydroxy-progesterone-caproate and intravaginal progesterone. There is evidence that synthetic and natural progestogens are not equivalent in their efficacy, indications and safety profile. Intramuscular and intravaginal progesterone have been used successfully in different patient populations[52]. For example, in women with previous preterm birth or second trimester miscarriage and current singleton pregnancy; women with short cervical length on TVS; multiple gestation and preterm birth[44, 47, 53-58]. Evidence supporting progestogen has emerged from two big RCTs. Fonseca et al reported a 44% of PTB before 34 weeks of gestation in 250 women with CL<15 mm at 20-25 weeks of gestation which was significant [RR 0.56; confidence interval (CI),0.36-0.86]. These data were subsequently supported by Hassan et al where the benefit of vaginal progesterone in 458 women with CL of 10-20 mm at 19-23 weeks of gestation in reducing of preterm birth before 33 weeks of gestation was confirmed (RR, 0.55; 95% CI,0.33-0.92)

The individual patient data meta-analysis performed in 2012 confirmed that administration of vaginal progesterone in asymptomatic women with CL < 25 mm significantly reduced risk of PTB occurring at 28 weeks to <35weeks, as well as neonatal mortality, incidence of RDS and admission to NNU. Since that its use has been widely used, especially in USA, in patients with singleton gestation and short cervix at mid-trimester scan. Some authors claimed that the significant reduction in the rate of PTB in USA was due to implemented recommendation to use progestogen[59]. The most recent evidence regarding the use of progesterone comes from the largest RCT, the OPPTIMUM trial, which tested vaginal

progesterone in 1228 women at risk of preterm birth. This study failed to find any evidence to support the use of progesterone in the entire population or in the subgroup of women with a CL < 25 mm. One of the criticisms of this trial was that, compliance with medication in the trial was only 69%[60] but this actually represents better compliance than usually seen in normal clinical practice[61]. A sub analysis looking at route of administration also showed no difference in outcomes.[62] OPPTIMUM was heavily criticised for lacking subgroup analysis as it can lead to minimising bias and identifying those groups of patients, if any, which may benefit from progesterone administration. Despite the trial showing no difference in overall reduction of PTB, there was a reduction in the occurrence of unwanted neonatal outcomes after the administration of progesterone (neonatal death, unadjusted OR 0·17, 95% CI 0·06–0·49; brain injury on ultrasound 0·50, 0·31–0·84). Disappointingly though these differences failed to show any identifiable improvement in child development when assessed at 2 years of age (cognitive score, progesterone group *vs* placebo group, 97·3 [SD 17·9] *vs* 97·7 [17·5]; difference in means −0·48, 95% CI −2·77 to 1·81).

Despite these results, some researchers continue to search for evidence supporting those methods of PTB prevention with in a single setting, randomising patients to pessary, progesterone or cerclage arms[63].

1.4 Cervical cerclage

1.4.1 Indications

Cervical cerclage has been offered to treat cervical insufficiency for over 60 years. One of the reasons for its continuous use is the lack of reliable evidence to support an alternative. Nevertheless, vaginal cervical cerclage is included in the interventions aimed to reduce rates of preterm birth specified in the “Born Too soon report” and occupies third place after

smoking reduction and decreasing multiple embryo transfers during assisted reproductive technologies.

The placement of suture is currently only considered for singleton pregnancies and is not recommended in twin/multiple pregnancies[64]. Women who present with history of midtrimester loss or previous preterm birth need to have a detailed history taken. Sometimes preterm birth can be due to placental abruption, iatrogenic or from multiple gestation so those cases have to be excluded from indications for cerclage.

Currently the UK cerclage practice is based on recommendations from NICE guideline on preterm birth[14]. This has three main indications for cerclage insertion: elective based history, proactive based on ultrasound criteria; and emergency/rescue cerclage. In US rescue cerclage is called physical-examination indicated cerclage.

Evidence for history-indicated cerclage mainly derives from a large MRC multicentre study[65] which recruited 1292 women who were deemed to be at high risk of cervical insufficiency and randomised them to cerclage (647 women) versus no intervention (645 women). The MRC trial was an equipoise trial. It has been criticised for only recruiting women with uncertain diagnosis of cervical insufficiency and in this way diluting the results, as they have excluded those at high risk. The inclusion criteria was based on their obstetricians uncertainty as to whether to recommend cervical cerclage as intervention. Most women had a history of early delivery or cervical surgery in the past. Results from this trial demonstrated that woman who had cerclage were less likely to have PTB < 33 weeks of gestation than those who didn't have any intervention (13% versus 17%) but there was no difference in fetal or neonatal outcome. The overall preterm delivery rate was 28% which is normally

observed in high risk population. 25 women needed to be treated to prevent one preterm delivery.

There were three more trials that looked at history indicated cerclage versus no intervention. Lazar et al[66] looked at insertion of cerclage versus no intervention in 506 women with cervical incompetence and showed no significant difference in preterm delivery rate (6.7% versus 5.5%). Rush et all[67] looked at outcomes of pregnancy in 194 women who had 2 or more previous preterm deliveries before 37 weeks of gestation again there was no difference in outcome (34% in cerclage group versus 34% in no cerclage group delivering before 37 weeks of gestation). Althuisius et al in CIPRACT trial[68] recruited women based on history suggestive of cervical incompetence. Women had TVS measurement of the cervix. Twenty-three women were randomised to prophylactic cerclage arm and 44 to no intervention group. The observational cohort had further random allocation to therapeutic cerclage and bed rest or bed rest alone when they had cervical shortening of <25 mm on transvaginal scan.

No significant difference was found between the prophylactic cerclage group and the observational group in preterm delivery <34 weeks' gestation (3/23 vs 6/44, respectively).

As a result, the current NICE guideline[14] recommends to offer history indicated cervical cerclage to women with history of three or more second trimester losses or preterm births. It doesn't recommend to offer intervention such as cerclage to women who had fewer than 2 SMTL or PTB. Ideally cerclage should be placed between 12 and 14 weeks of gestation in a planned elective manner. Currently there is no evidence to support pre-pregnancy tests for diagnosis of cervical insufficiency can be valuable in identifying women in whom history indicated cerclage can be beneficial. One observational study[69] looked at 175 women with history of midtrimester loss assessing patient's cervical resistance index. The consequent

cervical cerclage in these group of patients gave 75% successful pregnancy outcome, a result consistent with if conservative therapy would have been implemented. There was no control group either so no conclusions can be drawn[69].

Ultrasound indicated cerclage is offered to women with history of one or more SMTL or PTB whose cervix is found to be 25 mm or less on TVS. Four RCTs compared ultrasound indicated cerclage versus conservative management.

Berghella et al[70] randomised 61 women with the short cervix (25mm) to cerclage (n=31) versus no intervention (n=30). The primary outcome of the study was delivery before 35 weeks. There was no difference found in those who had cerclage (14/31) compared to those who had no intervention (14/30).

Rust et al[71] randomised 113 women with short cervix (<25 mm) to cerclage (n=55) versus expectant management (n=58). Again there was no significant difference in PTB rate between two groups (35% versus 36% respectively).

To et al[72] randomised 253 women with short cervix of<15 mm to cerclage (n=127) versus expectant management (n=126). The rate of PTB (delivery before 33 weeks) was similar in both groups. Cerclage group 28/127 versus 33/126 in control group (p=0.44).

And the last RCT, mentioned above, CIPRACT by Althusius et[68] al recruited women with obstetric history suggestive of cervical insufficiency. As a part of that large study 35 women were found to have a short cervix <25 mm on TVS. Of the 19 women who received a cerclage, none delivered before 34 weeks compared to 7/16 who had bed rest alone.

There is some scepticism regarding outcome of those trials because of few issues. Al three trials, for example, included low and high risk women. Rust and Berghella included twin pregnancies, where pathophysiology of PTB is different to singleton pregnancy and cervical

length measurement, which requires intervention could be different as well. Both Rust and Berghella included women who had cervical funnelling on the scan irrespective of cervical length. The funnelling is very subjective finding on TVS to compare with cervical length.

All studies took a cervical length “cut off” of 25 mm, apart from To et al who used “cut off” of 15 mm, which can skew the data significantly as the risk of PTB increases exponentially below this measurement.

The predicted probability of preterm delivery has been also linked to the cervical length. Berghella et al[73] has proven that gestational age at which cervical length is measured as well as the length itself has a significant impact on prediction of spontaneous preterm birth. The conclusion from their study was that the cervical length is inversely related to the risk of spontaneous preterm birth, women with the shortest cervical lengths have the highest rates of spontaneous preterm birth. Their analysis suggests that the risk of PTB before 35 weeks decreased by 6% for each additional millimetre of cervical length (odds ratio 0.94, 95% confidence interval, 0.92-0.95, p=0.01). A subsequent systematic review confirmed that the shorter the cervical length the higher the positive likelihood ratio for spontaneous PTB before 35 weeks of gestation[74].

As a result of this review cerclage can only be applied to an at risk population and is not recommended for women with a short cervix and no history of SMTL or PTB[75]. Thus women who have an incidental finding of a short cervix on a transvaginal ultrasound scan should not be offered cervical cerclage as there is a lack of evidence of benefit. Also, it is just the cervical length which should be taken into consideration on scanning and predicting the probability of the preterm birth not the cervical funnelling. Women with incidental finding of cervical funnelling on transvaginal scan should not be offered cerclage[64].

The final type of cerclage is called emergency cerclage or in American literature physician indicated cerclage. It is a cerclage which is offered to women when they are found to have a dilated cervix with fetal membranes bulging into the vagina. This suture is offered irrespective of cervical length or history of previous preterm birth. There have been a number of trials looking at outcomes of rescue cerclage. Overall rescue cerclage can prolong the pregnancy on average for 5 weeks when compared to conservative management. This evidence comes from more than 25 retrospective observational studies and one RCT. The RCT looked at outcomes of rescue cerclage versus bed rest alone[76]. The rescue cerclage was followed by administration of indomethacin and antibiotics. The rate of the preterm birth was lower in this group as well as composite neonatal mortality when compared with controls (53.8% vs. 100%, respectively, P=0.02). The most recent evidence[77] confirmed that antibiotics and indomethacin on their own made no difference to the prolongation of pregnancy.

1.4.2 The procedure

There are several types of cervical cerclage. Depending on the route of insertion of the stich, cerclage can be divided into abdominal and vaginal. Abdominal cerclage is now commonly performed laparoscopically or via mini-laparotomy. A robotic approach has recently been described. Transabdominal cerclage (TA) is now usually offered pre-conceptionally and only occasionally inserted at 10-12 weeks of gestation under general anaesthesia[78]. It is by definition a history indicated cerclage. The 2 main indications for transabdominal cerclage is offered when the vaginal route is not possible or vaginal cerclage has failed previously. There is one single RCT comparing TA history indicated cerclage versus TV history indicated cerclage. The incidence of preterm birth was significantly lower in TA group (18% versus 42%)[79].

The first operation described to treat cervical insufficiency was described by Lash A F and Lash S R and involved excision and repair of some part of the cervix, which they thought was leading to its weakness. The procedure fell into disrepute due to its high complication rate and subsequent incidence of infertility[80].

There are currently two surgical techniques used for vaginal insertion of cerclage. Both techniques carry the name of the doctors who invented them- Indian Dr Vithal Nagesh Shirodkar and Australian Dr Ian McDonald.

In 1951 Dr Shirodkar initially successfully placed a catgut purse-string suture in a woman with recurrent miscarriage. Later he realised that catgut dissolves quite quickly and may not be very suitable for the procedure which is aimed to strengthen the cervix for a long period of time. He subsequently modified his operation using a strip of the fascia lata with linen suture[81]. He filmed his operation and presented his technique for the first time in 1951 at the Silver Jubilee Celebration of the French Society of Gynaecology. The case was published later in 1955 and described the successful outcome of pregnancy where the Shirodkar suture was used in a woman with cervical insufficiency [82]. Two years later Dr I McDonald introduced a new technique[83], which is now most commonly used. The first time it was used in a patient with a dilated cervix and bulging membranes this was in fact an emergency cerclage. He placed initially a catgut suture and then repeated the procedure 3 times on the same patient with an interval of few weeks. The outcome was a live birth at 34 weeks of pregnancy. Later he used non-absorbable silk instead of catgut for the same reason as Shirodkar and achieved good results. Thirty-three out of 70 women, who had emergency cerclage between 20 and 24 weeks of gestation, had a live birth with surviving neonates. In the rest of the pregnancies neonates died of extreme prematurity even though the

pregnancy was prolonged for 3-4 weeks.[24] He published his retrospective series in the Journal of Obstetrics and Gynaecology of the British Empire in 1957.

In both techniques a purse string is placed around the cervix. The Shirodkar technique is more invasive as it requires reflection and hence dissection of the bladder, takes longer to perform and can lead to more complication at insertion and removal point. The cerclage procedure is performed in theatre under regional or general anaesthesia in aseptic technique.

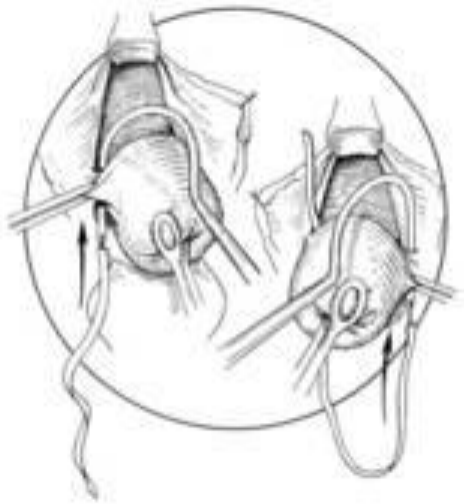


Figure 5. Insertion of the Shirodkar suture

Outcomes of different types of anaesthetics (general versus regional) were compared in an RCT of history-indicated cerclage with the Shirodkar suture. There was no difference in rates of preterm birth 11.8%(general) versus 15.0% (spinal) or rates of second trimester miscarriage 5.9% (general) versus 10% (spinal).[84] As the obstetric outcomes are the same and the safety profile for regional (spinal) anaesthesia is better, this method is now routinely recommended for the placement of a cerclage suture.

The patient is placed on the table in dorsal lithotomy position, cleaned and draped with good exposure of the whole cervix in order to avoid injury to the vaginal tissues. Different surgical retractors are used for those purposes.

Cleaning is performed with different solutions. Currently no data exists to confirm the efficacy of preoperative use of antimicrobial solutions versus none during cerclage procedure, although as data emerges about the microbiome, this in itself may become important. Usually chlorhexidine and povidone iodine are used if the patient has no allergies. Those

agents have been compared at the time of vaginal hysterectomy in RCT, where chlorhexidine was proven to be superior to povidone iodine, but it is unclear whether this can be applied to cerclage procedure[85].

- Currently the McDonald technique is the most commonly used procedure. The cerclage is placed at 12-14 weeks. A purse-string suture is placed round the cervix in 2-4 bites. The stich is placed anteriorly as close as possible to vesicocervical reflection and posteriorly as close as possible to uterosacral ligaments, capturing the stroma next to cervical canal[78], avoiding 3 and 9 o'clock positions because of underlying paracervical vessels. During this procedure the bladder and rectum are not reflected, so surgeons should be particularly careful not to put the stich through those structures[86]. Once the suture is placed, the knot is tied anteriorly or posteriorly, again according to surgeon's preference. The ends are left long enough to identify them later (usually 36-37 weeks of pregnancy) for removal.
- The Shirodkar cerclage is similar but more challenging, as it requires bladder dissection so technically more difficult than McDonald's method. The vesicocervical reflection is identified and mucosa over the anterior lip of the cervix is incised. The bladder is then mobilised via sharp and blunt dissection, the same as during vaginal hysterectomy, until the level of the internal os is reached. The cervix is grasped with ring forceps for traction and the mucosa on the posterior lip is incised in the same manner as in front to reflect the Pouch of Douglas and mobilize the rectum. A non-absorbable suture is placed posteriorly to anteriorly in the cervical stroma and tied anteriorly obscuring the internal cervical os. The incisions on the mucosa are closed with absorbable suture burying the cerclage stitch. The Shirodkar procedure

sometimes involves a permanent stitch around the cervix which will not be removed and therefore a Caesarean section is recommended as the method of delivery.

There have been several modifications to both methods of cerclage. For example, in Shirodkar cerclage knots should be placed posteriorly to avoid erosion into the bladder. Sometimes reflected mucosa are not sutured at the end of the procedure if haemostasis is adequate[86]. Surgeons used different sutures, a combination of different sutures and different types of needles. One of the most common modifications of Shirodkar suture is when the knot is buried under vaginal mucosa with a small part of the threads visible for removal. Quite often, the whole stitch is buried and patients go for elective caesarean section. Than the stich can be used for consecutive pregnancy if planned. If not, then suture is removed at the time of caesarean section under anaesthetic.

Cervical cerclage is usually a day case procedure but in some units, patients are kept overnight. Variations in practice include the prescription of indomethacin for 24-48 hours. Restriction on physical activity or vaginal intercourse is not evidence based. Patients are discharged home with advice on bleeding per vagina, leakage of fluid, fever or tightenings/contractions. The suture is usually removed at 36-37 weeks, in an outpatient setting, to prevent the risk of tear to the cervix in case the patient goes into labour. Few cases of severe cervical lacerations have been reported when cerclage was left in situ till the onset of labour[87]. In 6% of cases suture removal requires regional anaesthesia and removal in theatre. Removal of cerclage maybe considered earlier then 36 weeks in case of preterm pre-labour rupture of membranes (PPROM), vaginal bleeding, signs of chorioamnionitis or if delivery is recommended because of concurrent obstetrical or maternal medical conditions (for example pre-eclampsia)[88]. With regards to PPROM, there has been

only one RCT that compared retention of cerclage versus removal in cases of PPROM. In this study statistically significant differences were not detected in prolongation of pregnancy, infection, or composite neonatal outcomes. But there was less infectious morbidity noted associated with immediate removal of cerclage.

Initially a total of 142 patients should be included, based on sample size calculation. Interim analysis suggested that the conditional power for showing statistical significance after randomizing 142 patients for the primary outcome of prolonging pregnancy was 22.8%. So the study was terminated after a total of 56 subjects were randomized (32 for removal and 24 retention of cerclage). These findings "may not have met statistical significance if the original sample size of 142 was obtained, however they provide valuable data suggesting that there may be no advantage to retaining a cerclage after preterm premature rupture of membranes and a possibility of increased infection with cerclage retention[89]."

Few retrospective studies supported cerclage removal as it is associated with decreased levels of septic complications.

If patients with existing cerclage develop uterine activity at any stage of the pregnancy, reinforcement with another suture has not been proven to be of any benefit [90].

1.4.3 Type of suture material used

Several suture materials have been used to perform the cervical cerclage procedure including Mersilene 5mm tape [65, 91, 92], Mersilene silk[24], metal wire, human fascia lata[82], Prolene[71] and Nylon[68, 93-96]. Currently the most commonly used suture material is the Mersilene tape (a braided suture material/mesh) because of its perceived strength, reduced likelihood of tearing through tissues and ease of removal.

Implantable mesh devices have been used in surgery for a long time. Their use includes hernia repair, breast transplants and vascular surgery. Mesh is used in gynaecology mainly

for stress incontinence procedures and for prolapse surgery to give extra support to weak tissues. Modern use of mesh for the treatment of stress urinary incontinence (SUI) was described as tension free vaginal tape (TVT) procedure by Ulmstein in1997[97]. The eventual material choosen was a type I polypropylene woven mesh and became extremely popular and widely used in urogynaecology with minimal complication rate in lon-term follow-up studies[98]. High recurrence rate of vaginal prolapse after primary surgery combined with success of TVT mesh led to the development of use of mesh in POP procedures. There was evidence to prove a beneficial use of mesh in urogynaecological surgery but recently use of those mesh devices has been questioned[99] due to complications, such as erosion, expulsion, infection and pain, with mesh used for POP.[100]

There are two main types of mesh used for POP procedures : biological and synthetic or combination of different products. Biological derived from pig or cow tissue and non-absorbable/synthetic is usually made from polypropylene.

A first classification of synthetic meshes was suggested by Amid[101] and was based on physical characterisctics of mesh devices. Lichtenshtein Hernia Institute also categorises all mesh products used for surgical purposes into four categories[102].

Table 1. Types of mesh

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

Type IV mesh is not suitable to be used in soft tissues. Type II and Type III meshes are multifilament and have small pores which can confere a benefit to the smaller bacteria so they cannot be reached by the larger macrophages. As such a chronic infection[100] can occur; as a result several Type II and Type III meshes have been abandoned in urogynaecology and ophtalmology. When such multifilament meshes are placed in the vagina, they behave like a wick[103], allowing bacteria to travel up the mesh. Lilly in 1968 noticed the same effect happens in the oral cavity. When tissues are sutured with monofilament sutures (MOS) it causes less inflammatory reaction compared to multifilament (MUS) suture[104]. His hypothesis was supported later by Katz and Evans. They claimed that physical characteristics of suture material may be a major determinant of tissue response[105]. Lilly suggested that bacteria and oral fluids may be transmitted into a wound by a "wicking" action that would be more active in MUS than MOS.[104] A very similar effect happens in the vaginal "cavity", where vaginal secretions are drawn up all way through the mesh. Not only the structure of the mesh is important but also the environment it is exposed to has a major role. For example, Mersilene® (Type III mesh) has been used in a clinical study looking at POP surgery. In this study the patients underwent a sacrocolpopexy with the mesh which was placed either abdominally or vaginally. The abdominal group had a 3% erosion rate whilst the vaginal branch had almost a 20% erosion rate[106].

Type I meshes have monofilament fibres and large pores (> 90 microns). As a result it allows macrophages to get into the pores and speeds up the process of angiogenesis. As a consequence an initial inflammatory response settles quickly and leads to the formation of fibrous tissue around the mesh[103]. This leads to a low level of infection and erosion/extrusion. The majority of meshes used in stress urinary incontinence (SUI) and POP surgery are of Amid Type I[100].

As a result of complications with mesh the FDA warned against mesh products specifically Type II and Type III meshes. It also led to certain recommendations from RCOG regarding issues of mesh insertion and removal. NICE also currently supports the use of mesh for abdominal surgery for apical vaginal support as long as there are also arrangements for clinical governance, audit and consent.

Any complications associated with mesh in mandated to be reported to Medicines Healthcare products Regulatory Agency (MHRA) as mesh is considered the medical device.

As mentioned before, multifilament and braided sutures have been associated with an increased risk of infection especially when used in potentially non-sterile surgical fields [33]. If the wick- effect produced by spaces between the suture strands happens around the cervix, it can lead to ascending genital tract infection, chronic cervical inflammation and chorioamnionitis due to the optimal environment for bacteria to multiply. Chronic inflammation takes place around the cervix. As a result, these multifilamentous mesh materials create a chronic inflammatory response, which ultimately results in the mesh becoming encapsulated in surrounding tissues and not being incorporated into them. The combination of encapsulation and the tail of the tape acting as a route for ascending infection result in the mesh being surrounded by an inflammatory exudate and ironically allows the mesh to be removed with relative ease and in one piece [34] which is the reason type one meshes cannot be used as they would be incorporated into the cervical tissue and could not be removed.

There is no clear evidence to date with regards to type of suture material to be used for cervical cerclage[39]. Currently the majority of the obstetricians use Mersilene tape (braided tape, Type III). This practice is not supported by any evidence and is often determined by

personal choice or historical teaching. Mersilene tape is popular for its strength and relatively non-complicated removal. As it is a braidedsuture, it can stimulate a chronic inflammatory response and later be encapsulated, hencewhy it is easy to remove in one piece once the knot is cut. However , Mersilene has high absorbent properties and so acts as a wick. This wick may provide an environment where bacteria can grow and a route by which they can travel and enter the uterus where they may cause a chronic infection and stimulate early labour. The wick-effect of the multifilament material was confirmed by studies on Dalcon Shield, the IUD which was banned from use in 1970s because of the high rate of complications especially infection. Studies confirmed that multifilament thread, which consisted of 200-400 individual filaments, used in Dalcon Shield extended down into the vagina and was found to have a wicking effect in which bacteria-contaminated fluids were transported from the vagina into the uterus.

The presence of multifilament braided suture material in the cervix when cerclage is placed predisposes to inflammation around the cervix, ascending infection which can lead to chorioamnionitis and in turn precipitates preterm birth. There are some studies confirming that microorganisms in the vagina are similar to those in amniotic sac in cases of chorioamnionitis. There are reports of an increased frequency of chorioamnionitis in premature cervical dilatation[107] and increased risk of puerpal fever which is associated with cerclage[65]. It is well documented that identified infection, both acute and low grade, is the risk factor for preterm birth in almost 50% of cases[108]. Infection can spread haematogenously or via ascending route from the vagina. During healthy pregnancy fetus is protected from the ascending infection by several mechanisms and barriers. Firstly, the cervix which holds a mucus plug containing antibacterial substances[109]. This plug protects the sterile uterine environment from the vagina, which is full of bacteria. It has been named

“a gate keeper” by some authors[110] which claim there is an association between impaired function of the cervical plug and preterm birth. A cervical mucous plug is approximately 10g in weight, is produced by secretory cells in the endocervical canal where the plug is located in pregnancy. The cervical plug contains mucins (large glycoproteins). They prevent diffusion of bacteria and inhibit viral replication. Also, a mucosal plug has immunological properties which can arrest bacterial infection by stimulating a robust inflammatory response. Besides all that, a cervical plug contains numerous antibacterial substances such as lysozyme, antimicrobial polypeptides, lactoferrin, calprotectin, alfa-defensin and betta-defensin. When their concentration is low it may predispose to the onset of preterm labour or premature rupture of membranes followed by preterm delivery[109].

The suspected wicking and associated peri-cervical infection as a result of Mersilene is prompting many specialists to move towards the adoption of monofilament sutures such as Prolene or Nylon. Conversely monofilament sutures are thought to be weaker and can possibly traumatise the cervix at the time of insertion and removal. But ironically in surgery, if there is concern about tissues one would opt for a monofilament, so the argument in terms of less trauma at insertion is theoretically flawed, but the arguemnt of the monofilament “cheese wiring” or cutting through the cervix in the presence of inflammation remains.

To date the characteristics associated with these meshes or tapes have not been considered with regards for the potential for the Mersilene® tape to contribute to premature delivery.

1.5 Research hypothesis

Therefore, I have hypothesized that any increased risk of infection and chronic inflammation around the cervix associated with a braided suture material such as Mersilene tape could be a major confounding factor for underestimating the true benefit of cervical cerclage[39]. I

hypothesised that as braided sutures would have been the predominant type of suture used in the studies included in the Cochrane report, they may have unintentionally induced a bias in the conclusions and possibly masked a real benefit of cervical cerclage. It is possible that some obstetricians are aware of or suspect this link and that is why they prefer to use non-braided monofilament sutures such as Nylon or Prolene for the cervical cerclage. Our survey findings (see *chapter 5*) confirm that almost one in five obstetricians performing cervical cerclage use monofilament sutures. But this choice is not evidence-based. The impact of suture material on the outcome of a surgical procedure should not be ignored. There are examples in medical literature where change of type of suture material has unmasked the effectiveness of the surgical procedure which was previously unrecognised[111]. In the Cochrane review by Kettle et al change of suture material, (use of synthetic sutures instead of catgut[111]), was associated with less perineal pain and analgesia requirements ten days postnatally, after episiotomy and second degree tears. Women who had synthetic sutures used for second degree tear repair had less re-suturing episodes. The lack of clear and widely accepted criteria for inserting a cerclage is another possible reason for the inability of the current literature to demonstrate a clinical benefit of cerclage procedures.

Up to this day researchers have investigated different aspects of cerclage procedure in relation to the type of procedure (McDonald or Shirodkar), number of sutures places (one versus two), timing of the procedure (at which gestation it is the best to insert the suture) and eligibility criteria for insertion[112-114]. Some researchers did look at outcomes of pregnancy depending on different type of suture material used in cerclage, but they didn't include monofilament sutures[96]. For example, Berghella et al looked at the outcomes of pregnancies in patients with ultrasound indicated cerclage, comparing Polyester braided thread (Mersilene or Ethibond) and polyester braided Mersilene tape. Both sutures had the

same efficacy[96]. So to our knowledge no published RCT or NRS has compared the use of braided suture materials to non-braided monofilament sutures.

In order to test my hypothesis few steps were undertaken.

1. Initially a retrospective analysis of the cohort of pregnant women who had cervical cerclage with Nylon (monofilament non-braided) and Mersilene (braided) in two units in the UK. This analysis revealed that use of Nylon is associated with higher rates of successful pregnancies (95% compared to 88% respectively) - *Chapter 2*. However, it was a retrospective study and it is well known that non-randomised studies evaluating an effectiveness of a surgical procedure are prone to potential bias and overoptimistic results regarding a new technique or new therapy[115].
2. In collaboration with Birmingham Clinical Trials Unit (BCTU) and the RCOG I have conducted a national survey of O&G Consultants in the UK, which confirmed variability in practice. The majority of respondents were using Multifilament (braided) sutures and only 13% used Monofilament sutures. The second important observation was that 75% of respondents were not sure about which suture material is best to use - *Chapter 4.*
3. We have undertaken systematic reviews, which identified no RCTs that have addressed this question. Therefore, we extended our review to include all types of studies with no language or time restriction. A meta-analysis of non-RCT studies investigating cerclage outcome by type of suture material used demonstrated that monofilament cervical suture is associated with a significant risk reduction in associated pregnancy loss compared to multifilament/braided sutures (RR 0.32 95% CI 0.19 - 0.53) - *Chapter 3*.

Chapter 2- Retrospective data analysis

2.1 Objectives

The concerns raised in relation to specific multifilament meshes in respect of gynaecological and surgical practice have not led to an awareness of the potential problems of their use in obstetrics, nor has there been any apparent change of practice in obstetrics. With the support of colleagues from Addenbrookes Hospital, I performed a retrospective review of elective cervical cerclage carried out in two large UK teaching hospitals (Birmingham Women's Hospital and Addenbrookes Hospital). The main objective of this review was to study the outcomes of singleton pregnancies considered to be at risk of preterm delivery or midtrimester loss in relation to the two suture materials used, Prolene and Mersilene tape.

In the first Unit (Birmingham Women's Hospital NHS Foundation Trust) only a few Consultants were involved in performing cervical cerclage and used either Mersilene tape or Prolene suture. The majority of the Consultants in Birmingham used the McDonald technique for cervical cerclage. The role of Shirodkar cerclage was reserved predominantly for the patients with previous failed McDonald cerclage, short cervixes after previous treatment (LLETZ, cone excision et cetera). In Addenbrookes Hospital only two Consultants performed cervical cerclage. One routinely used Mersilene tape and the other Prolene suture.

2.2 Methods

Obstetric theatre databases were hand searched to identify patients who had undergone cervical cerclage. The data was cross referenced with the Obstetric databases at both centres. Notes were identified where possible and details collected on an anonymised proforma (**see Appendix 1**). Data from other hospitals was sought if delivery occurred in

units other than the hospital where the cervical cerclage took place. No attempt was made to stratify for the complexity of the case or control for other confounding variables.

Information about the procedure including cerclage type, suture material used, gestation at insertion, indication for insertion and nonviable birth (stillbirth or miscarriage) was collected. Other data collected included gestation at removal; gestation at delivery; mode of delivery; previous preterm birth or midtrimester loss; indication for cerclage; and relevant microbiological data.

Outcome was defined as either:

A composite of fetal demise prior to delivery or nonviable birth (delivery < 24 weeks of gestation or intrauterine death) delivery before 34 weeks of gestation.

Analysis was performed using Graphpad Instat 3.06. Intergroup comparisons for continuous variables with a non-parametric distribution were made using the Mann-Whitney U test to determine significant differences between the data sets. For such data, median values and 95% confidence interval (CI) are described. Categorical data was analysed using Fisher's exact test and odds ratios and 95% CI. Significance was taken as $P<0.05$ unless otherwise stated.

2.3 Results

Data were collected between January 2002 and December 2008 and 102 cases of elective cervical cerclage were identified. There was no record of suture material used in two patients and one had an abdominal cerclage procedure. No outcome data was available due to pregnancies delivering elsewhere and being lost to follow up in a further three cases. Thus ninety-six cases of elective cerclage had sufficient data and were analysed.

In majority of cases the procedure was performed by a Consultant. Even when it was performed by sub-speciality trainee (SST) or Registrar, it was under direct supervision of a Consultant, according to the notes **Fig 6.** In some notes this information was missing.

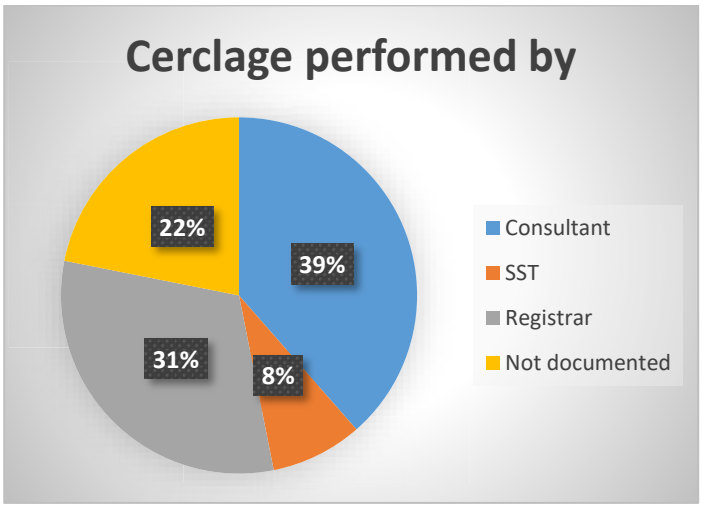


Figure 6. Grade of operating surgeon

Of 96 elective cerclage cases, forty underwent cerclage with monofilament Prolene® non-absorbable suture (41.6%) and fifty-six had Mersilene tape inserted (58.4%) **Fig 7.**

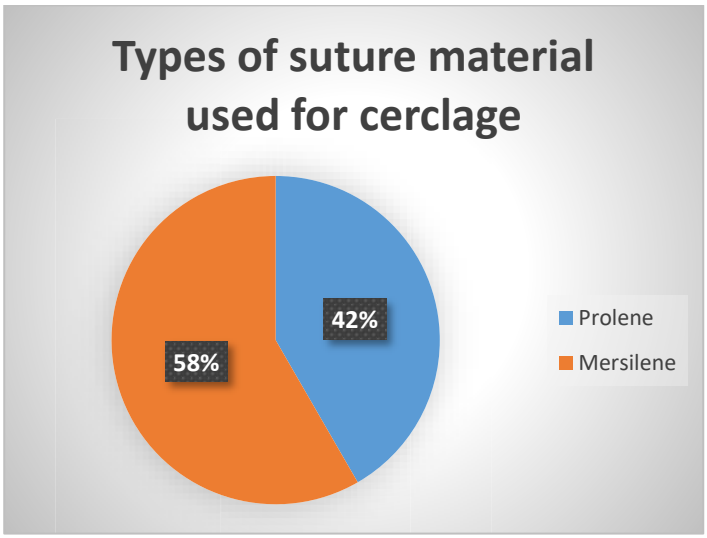


Figure 7. Type of suture material

For descriptive purposes we include details of the cerclage performed. Twenty-two were Shirodkar (22.9%) and seventy-four McDonald cerclage (77.1%) **Fig 8.**

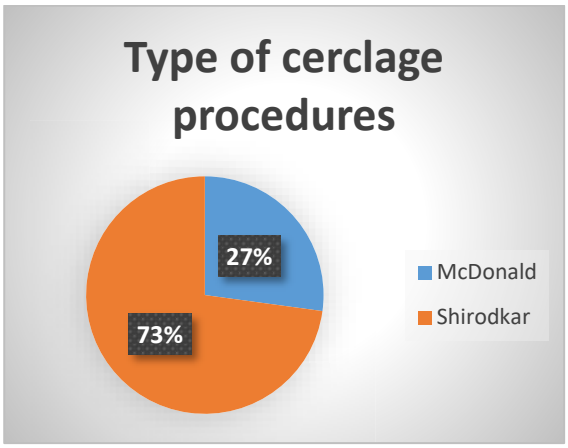


Figure 8. Type of cerclage procedures

Of the twenty-two Shirodkar cerclage, eleven (50%) had a monofilament Prolene® suture and 11 had Mersilene tape insertion (50%). **Fig 9**. In the pregnancies undergoing MacDonald cerclage, twenty-nine had a monofilament Prolene® suture (39.2%) and forty-five Mersilene tape (60.8%). **Fig 9.**

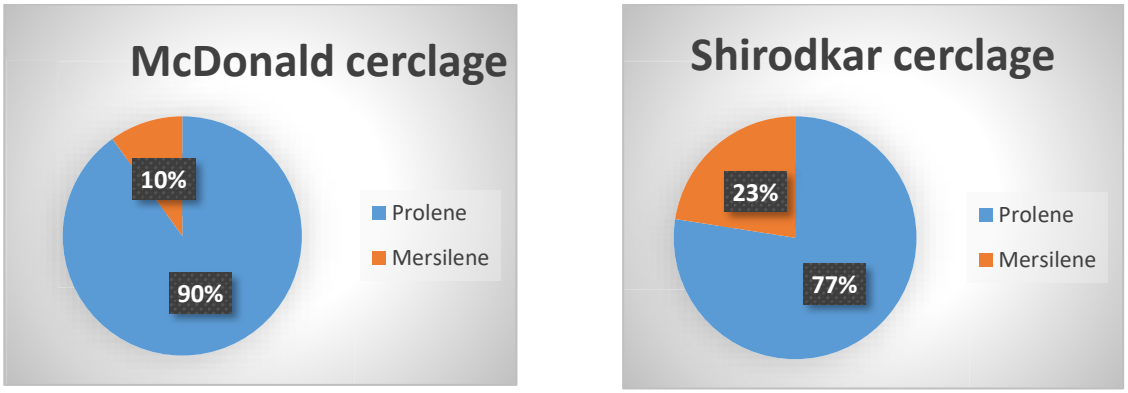


Figure 9.Types of suture material depending on cerclage technique

Thirty-eight of the forty patients who underwent Prolene® suture cerclage had live born children. In one, there was an intrauterine death (IUD) at 19 weeks and in the second, emergency Caesarean at 25+2 weeks with neonatal demise. Data was available on all forty patients who had undergone cerclage with Prolene® suture in relation to gestational age at delivery. Thirty-two (80%) delivered at a gestation over 34 completed weeks. In five cases, delivery was between 25-29 weeks (median 28 weeks [95% CI 24.7-29.3]) and there was on early neonatal death at 25+2/40 (20%).

We could only retrieve data from maternal notes, as a result documented follow up was only up until discharge. We didn't have access to neonatal data so late neonatal deaths, if any, were not included in this analysis.

So in those women who had Prolene inserted for cerclage there was a **95%** take home baby rate.

Of the 56 women undergoing Mersilene suture cerclage, forty-nine had live babies, seven had fetal demise. In these cases, 6/7 (85.7%) ended in miscarriage and 14.3% (1/7) in stillbirth at a gestation of 29+5/40 weeks (95% CI 16.7-23.9). Of these seven cases, the mean time of suture insertion to identified fetal demise was 6.5 weeks (range).

In summary those patients who had Mersilene used for cerclage had "take home baby" rate of **87.5%. Table 2.**

Based on our results, Prolene suture cerclage appears to be associated with **5%** risk of fetal demise and Mersilene suture a **12.5%** risk of fetal demise (Fishers exact p=0.2). By operation type, 1/22 (4.5%) patients undergoing Shirodkar cerclage suffered perinatal loss compared with 6/73(8.2%) undergoing McDonald cerclage (Fishers exact p=1).

Table 2. Demographic data and perinatal outcome in both suture types

	Multifilament suture n=56/102 (58.4%)	Monofilament suture n=40/102 (41.6%)
Age	Mean age 30.3 (range 46-28)	Mean age 35.8 (range 48-31)
Parity	Mean 2 (range 0-4)	Mean 2.3 (range 0-5)
Indication for cerclage	All Elective	All Elective
Gestation at insertion	Mean 13.2/40 weeks	Mean 14.3/40 weeks
Type of procedure Shirodkar	N=11/56	N=11/40
Type of procedure McDonald	N=45/56	N=29/40
Gestation at removal	Mean 36.3/40 weeks	Mean 36/40 weeks
Viable (live)	N=49/56	N=38/40
Delivery >34/40	N=41/56	N=32/40
Delivery <34/40	N=7/56	N=8/40
Non-viable	N=7(6 midtrimester loss+1 stillbirth), 7/56 (12%)	N=2 (1midtrimester loss+ 1 neonatal death), 2/40 (50%)
Gestation at delivery	Mean 35/40 weeks	Mean 35+3/40 weeks
Mode of delivery	C/S – 16/50 NVD – 34/50	C/S – 12/39 NVD – 26/39
Take home baby rate	N=49/56 (87.5%)	N=38/40 (95%)

We have looked at data on evidence of infection in the women where there was a reason to be clinically suspicious. In the monofilament group eleven (27.5%) patients had no swabs taken. Of those forty who had a swab; twenty (50%) had no growth. The remaining nine (22.5%) had positive cultures: six had group B haemolytic streptococcus, two had evidence of bacterial vaginosis and one had candida.

Of the Mersilene group twenty-two (40%) did not have any microbiological data available; of those that did, seventeen (31%) had no growth, eight (15%) had group B haemolytic streptococcus, five (9%) had Candida Albicans, two had bacterial vaginosis, one had evidence of unspecified anaerobic infection and one had Actinomyces. **Fig 10.**

Table 3. Microbiological data

Type of suture	No swabs taken	No growth	Positive cultures
Prolene/Nylon N=40	N=11 (27.5%)	N=20 (50%)	N=9 (22.5%)
Mersilene tape N=56	N=22 (40%)	N=17 (31%)	N=17 (30 %)

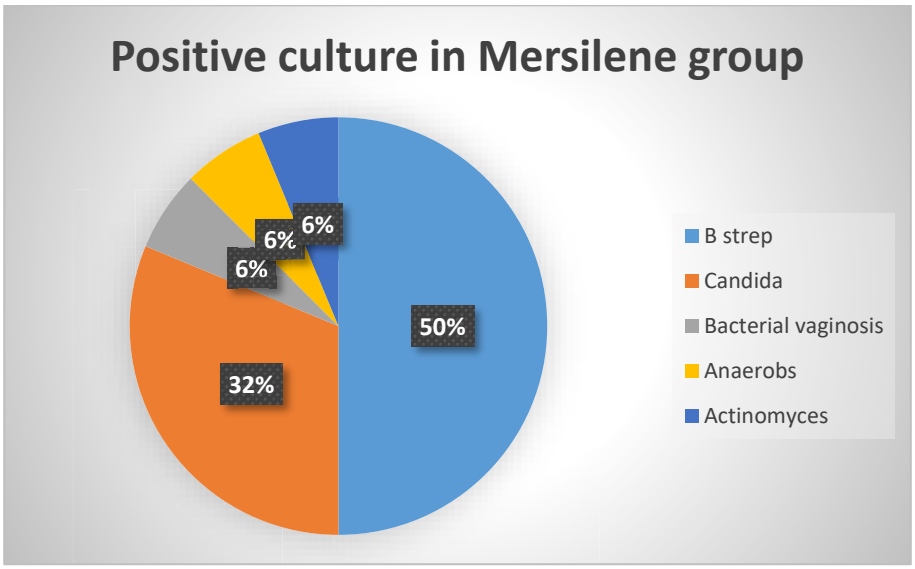


Figure 10. Results of positive microbiological swabs in Mersilene group.

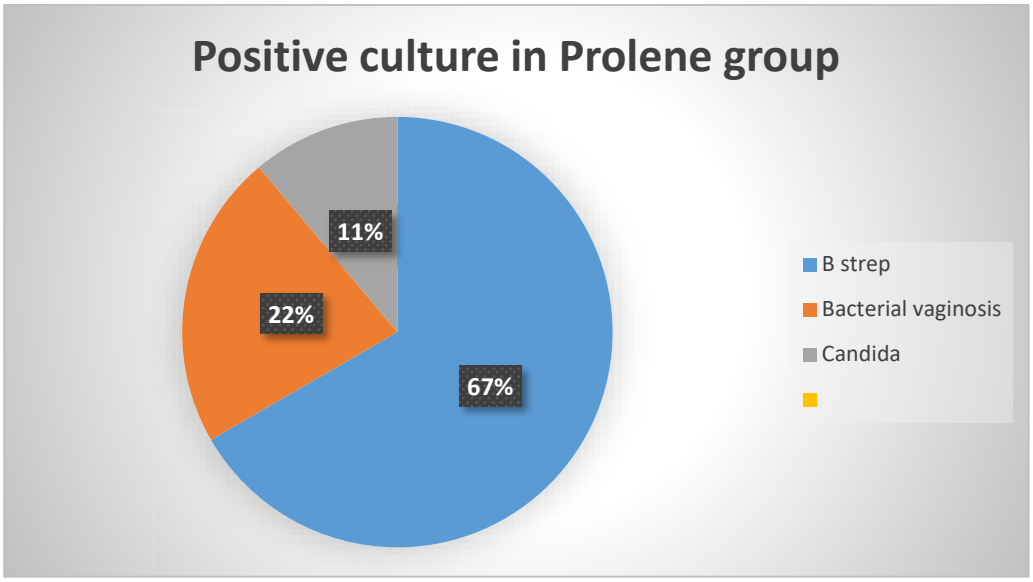


Figure 11. Results of positive microbiological swabs in Prolene group

In the monofilament group who delivered prematurely (7) (<34 week delivery) two had group B haemolytic streptococcus, five had no growth. In the Mersilene group, who delivered prematurely two had Candida Albicans, one had bacterial vaginosis, four had no growth and three had no microbiological data available.

There was no difference in the incidence of positive microbiology in the women who delivered before thirty-four weeks and those which delivered after thirty-four weeks.

2.4 Discussion

Our study was limited by its retrospective nature and the relatively small number of cases. However, even with small numbers, it did reveal a significant difference in fetal loss depending on type of suture material used (12.5% versus 5% with Multifilament and Monofilament groups respectively).

As mentioned in the previous chapter, there are good reasons as to why experience with monofilament and multifilament mesh and sutures in other areas of medicine might be

pertinent to obstetric surgery. Common complications of multifilament meshes, such as infection and erosion, may suggest that the use of Mersilene tape leads to an alteration in the integrity of the native cervical tissue. It also predisposes to an ascending infection and also because of the mesh construction may prevent the host tissue's ability to mount an appropriate defence against bacteria. Chronic inflammation around the cervix may be implicated in a weakening of the cervical and para-cervical tissues and in particular would explain the increased puerperal fever seen in previous reports of cervical cerclage[65]. Monofilament and Multifilament sutures display similar characteristics to the mesh implants. In addition, multifilament sutures demonstrate a potential for increasing capillarity characteristics which may increase fluid and bacterial movement, potentially increasing the risk of ascending genital tract infection, chronic cervical inflammation and chorioamnionitis.

Retrospective studies usually have errors due to confounding factors and bias. The most significant confounding factors was absence of information in all the notes on previous cervical surgery such as LLETZ procedures, previous cerclages and information about concurrent medication used before or after cerclage, for example Cyclogest pessaries. The insertion of the cervical suture wasn't standardised procedure and possibly could have varied operator dependant. Majority of the trainees (SSTs and Registrars) used Mersilene tape whether Consultants involved in cerclage service were using Monofilament suture more frequently. Potentially skills of the operating surgeon could have influenced the outcome as well. Again due to retrospective nature of the review information about technique of cerclage procedure itself and grade of the operating surgeon wasn't recorded in every set of notes.

The main strength of this review was that it was conducted relatively quick initially and during preparation for HTA, without significant expenditures which is one of the main advantages of these type of studies.

I have achieved the main objective of this retrospective review which was to look at the outcomes of pregnancies depending on type of suture material used in cerclage procedure to prevent preterm delivery or midtrimester loss. Based on the findings of this retrospective analysis, we hypothesised that increased risk of infection and pericervical mesh inflammation is associated with braided suture material, such as Mersilene tape, used for cerclage and can be a significant confounding factor for the underestimation the true effectiveness of the cervical cerclage procedure.

In order to support our research hypothesis based on this retrospective analysis of a cohort of pregnant women who had cervical cerclage using either Nylon (Monofilament) or Mersilene (Multifilament) where the former was associated with higher rates of successful pregnancies, I have undertaken a systematic review of the medical literature for both randomised and non-randomised observational and cohort studies that investigated cerclage outcome by the type of suture material used. This is presented in the next chapter.

2.5 Conclusion

In preparation for an application to Health Technology Assessment (HTA), I have extended retrospective data analysis to December 2012 and looked through an additional one hundred and fifty-six notes. The results of additional data (only one hundred and five cases included after data clearing) were combined with similar data from another five UK University hospitals giving a total number of six hundred and seventy-one women who had planned cervical cerclage. The data was published recently[116]. The results of retrospective analysis re-confirmed that in women receiving cerclage with Mersilene tape there are higher rates of

fetal demise (intrauterine death and delivery before twenty-four weeks) when compared with those receiving the monofilament suture (15% versus 5% respectively; $p<0.0001$) as well as preterm labour (28% Mersilene versus 17% Monofilament sutures; $p<0.0001$).

Chapter 3-Systematic review

Use of different suture material multifilament braided sutures versus monofilament non-braided sutures in planned (elective) cervical cerclage: Systematic review and meta-analysis

3.1 Objectives

1. To systematically review the literature to identify different types of suture material used for planned/elective (history-indicated, ultrasound indicated) vaginal cervical cerclage
2. To systematically review, and if possible, to meta-analyse data from the literature to determine pregnancy outcomes depending on type of suture material used in planned/elective vaginal cervical cerclage
3. To systematically review, and if possible, to meta-analyse data from the literature to identify adverse outcomes associated with cerclage especially rates of pregnancy loss and infection
4. To use the findings of this review in order to support the hypothesis for this thesis and development of research protocol for COTS pilot/feasibility study

3.2 Abstract

Objective

To determine the effectiveness of different suture materials used in planned/elective (history or ultrasound indicated) cervical cerclage.

Methods

Studies were identified through systematic search without language restrictions from MEDLINE (inception to 2016), EMBASE (inception to 2016), CINAHL and Cochrane Library, and manual searching of bibliographies of known primary and review articles. Studies were selected if women with previous pregnancy loss or history of preterm birth had history indicated or ultrasound indicated vaginal cervical cerclage. In a view of absence of RCTs comparing type of suture material in relation to planned/elective cerclage the search was extended to non-randomised studies (NRS) such as observational studies and case series were included. Data were extracted on study characteristics, quality and the outcome such as pregnancy loss. Relative risks from individual studies were meta-analysed using random and fixed effects models. Heterogeneity was evaluated graphically using forest plots and statistically using the I^2 statistic.

Results

The NRS meta-analysis demonstrated that non-braided sutures, compared to braided, were associated with a pregnancy loss rate of 4% compared to 15% respectively (RR 0.32 95% CI 0.19 - 0.53).

Conclusion

The NRS meta-analysis demonstrated that there is evidence to suggest that pregnancy loss is less in women undergoing planned (elective) cervical cerclage when un-braided

monofilament suture material is used. This review was limited by the quality, number and size of included studies. Also, there is no doubt that studies which do not involve randomisation are liable to potential bias. Hence there is a need for a randomised controlled trial to address this issue.

3.3 Introduction

Preterm birth remains the leading cause for perinatal mortality and morbidity worldwide with colossal implications for healthcare costs and the affected families caring for children affected by mental and physical disabilities as a result of PTB. Management of preterm birth remains one of the most challenging areas of modern obstetrics. There are few interventions, specified recently in Born Too Soon report, which have improved outcome of the PTB. Cervical cerclage was one of them and occupied the third place after smoking cessation and decreasing multiple embryo transfer during assisted reproductive technologies. It has been used for this purpose for decades. Recently it has become more popular especially in a view of flawed evidence related to Arabin pessary and findings from OPTIMUM confirming[60] that progesterone is not effective in the second trimester to prevent pregnancy loss. Irrespective of that some researches are still trying to compare all three treatments in single study (SuPPoRT trial)[63]. It has been proven that cervical cerclage can be very effective, especially in women with a history of previous PTB and/or short cervix on transvaginal scan. It reduces the rate of PTB in this cohort of women up to 20%.

In the UK cerclage is offered to women at risk of PTB or mid-trimester loss, as per the NICE recommendations[14], but the evidence from the recent survey states that quite often that practice can be sparse, not evidence based and often completely relies on personal preferences of the obstetrician involved, regarding patient selection, gestation at insertion and preferences on suture material used during the procedure, even though the perceived “golden standard” is Mersilene braided tape. So, there is a lack of consensus regarding several aspects of the procedure: timing of insertion (pre-conception, in first trimester ultrasound indicated or history based); optimal technique for cerclage insertion (vaginal or abdominal; if vaginal then Shirodkar or McDonald (both proven to be equally efficacious in

women with short cervixes); low or high; single/double sutures/pursue string; position of the knot anterior or posterior; type of suture material used. The mechanism of action for cerclage is also poorly understood but there is a theory that suture itself provides a mechanical support as well as keeping the cervical plug intact from ascending bacteria, thus protecting the fetal membranes from rupturing. Cervical cerclage is associated with infection and it is clearly stated in the first randomised trial on cerclage from 30 years ago as well recent data from Cochrane review. Possibly type of suture material used in procedure can play a role? It has already been proven in other disciplines that type of suture material can have significant impact on the outcome of surgical procedure.

Cervical cerclage remains the primary choice of treatment in many specialised preterm birth clinics and is an increasingly performed procedure. It is identified in the “Born Too Soon” report by World Health Organisation (WHO) as one of the five most important interventions to prevent preterm birth. Based on the WHO survey results 45% of Consultants in Preterm Birth specialised clinics in UK use cervical cerclage as their primary choice of treatment in women at risk. The NICE supports the use of cervical cerclage in a selected population[14]. Several techniques have been advocated for the insertion of a suture but the most popular ones are McDonald and Shirodkar when suture is placed around the cervix with or without bladder dissection with intention to prevent dilatation, keep mucosal plug in situ and prevent anticipated midtrimester miscarriage or preterm birth. Traditionally Mersiline suture has been used for cervical cerclage but monofilament sutures such as Prolene or Nylon are also in use even though not so popular due to technical difficulties of insertion and removal as well as the theory that it may not provide as effective mechanical support as a wide and strong Mersilene tape. As discussed in chapter 1, section 1.3, meshes especially braided ones are

associated with high risk of infection and guidance has been issued to restrict or prohibit their use in many surgical specialties.

A question of safety of cervical cerclage has been raised many decades ago in an MRC study[65] where cases of puerpal fever were reported associated with cerclage. Type of suture material used for cerclage 30 years ago wasn't considered as a possible cause of infection associated with cervical cerclage. There is a recent evidence supporting link between cerclage and infection. A systematic review by Saccone et al[117] also raised concerns about safety of this surgical obstetric intervention.

The aim of this review was to systematically analyse the available literature to assess the outcomes of pregnancies where women had planned/elective vaginal cervical cerclage, depending on type of suture material used during the procedure and to identify where use of multifilament braided sutures versus monofilament un-braided sutures has any impact on pregnancy loss.

3.4 Methods

3.4.1 Identification of literature

We searched databases for relevant published literature on outcomes of planned/elective cervical cerclage depending on type of suture material used during the procedure, with particular attention to pregnancy loss. We searched the following electronic databases: MEDLINE (from inception to November 2016), EMBASE (from inception to November 2016) and Cochrane Central Register of Controlled Trials (CENTRAL). A search strategy was carried out based on the following key words and/or medical subject heading (MeSH) terminology: 'cervical cerclage'; 'elective cerclage'; 'uterine cervix cerclage', 'vaginal cerclage'; 'short cervix'; 'sutures for cerclage', 'sutures'. Key words were combined using

AND/OR. I did not include term rescue cerclage as we only were interested in the outcomes of planned cervical cerclages, those performed as indicated on transvaginal ultrasound scan because of shortening cervix or history based ones. Rescue cerclage is performed when patient presents with a dilated cervix and membranes bulging into vagina.

Electronic searches were complemented by hand searches. In addition, references from all identified articles were checked. The search was not restricted by language. The searches were conducted independently by FI and another reviewer HH.

3.4.2 Study selection

Studies were selected if the target population were women who had a cervical cerclage. All articles about emergency cerclage as well as laparoscopic cerclage were excluded from the start, i.e only elective (planned) vaginal cerclage procedures were included. The primary outcome was defined as pregnancy loss depending on type of suture material used. The pregnancy loss was defined as second trimester miscarriage, intrauterine death in pregnancies where cervical cerclage was inserted or early neonatal death.

Table 4. PICO table

Acronym	Definition	Description
P	patient or problem	Women who had cervical cerclage
I	Intervention	Monofilament suture
C	control or comparison	Multifilament suture
O	Outcome	pregnancy loss

First, the titles and abstracts from the electronic searches were scrutinized by two reviewers independently (HH and FI) and full manuscripts of all citations that were likely to meet the predefined selection criteria were obtained. All case reports, letters to editor and commentaries were excluded. A final decision on inclusion or exclusion was made by two reviewers on examination of the full manuscripts. In cases of duplicate publication, the most recent and complete versions were selected. There were no disagreements about inclusion but the plan was such a case to occur was review by third potential reviewer (PTH) with resolution by arbitration. Data extraction was performed in duplicate by HH and FI. Information was extracted from each selected article such as study characteristics, quality and outcome data and entered on to a data extraction form.

3.4.3 Methodological quality assessment

We were unable to identify any RCT comparing type of suture material used for cerclage, so NRSs were used alone. The studies were assessed and selected using the Newcastle-Ottawa Scale (NOS)[118] which is commonly used as an assessment tool for non-randomised studies, especially cohort ones and case-control. Assessment criteria for case-controlled and cohort studies are different but they all cover 3-4 main domains such as the selection of participants, comparability of cohorts and the ascertainment of exposure (for case–control studies) or outcome of interest (for cohort studies). Stars are used to rate the quality of each criteria in the domain. One star is awarded as maximum for all items except for comparability where a maximum of two stars can be given. This assumes that all items included into Newcastle-Ottawa Scale have equal weight. The score ranged from 0 to 9, with a score of either 0 or 1 for each item.

The scale was developed by two big Universities one in Australia- University of Newcastle and the other one in Canada, Ottawa University. The first time scale was presented more than 10 years ago in Oxford, UK at the Third Symposium for Systematic reviews[119] and now has a full support of The Cochrane Collaboration for the use of non-randomised studies[120].

All selected studies were evaluated for:

- **Selection:** 1) representativeness of the exposed cohort; 2) selection of the non-exposed cohort; 3) ascertainment of exposure; 4) demonstration that outcome of interest was not present at start of study.
- **Comparability:** 1) comparability of cohorts on the basis of the design or analysis
- **Outcome:** 1) assessment of outcome; 2) was follow up long enough for outcomes to occur; 3) adequacy of follow up of cohorts.

The risk of bias was considered as **low** if a study gathered four stars for selection, two for comparability and three for ascertainment of exposure. The risk of bias was **medium** if study had two or three stars for selection, one for comparability and two for exposure. The **high** risk of bias was granted if study was scoring zero stars for selection, comparability or exposure.

We planned to use quality assessment in subgroup analysis to explain any observed heterogeneity. To detect publication and related bias, we were planning to do funnel plot analysis using Egger's tests to evaluate asymmetry.

3.4.4 Data synthesis

A data extraction form was designed to retrieve relevant information from selected studies. The second reviewer (HH) extracted data using the agreed form. Any disagreements were resolved by discussion.

Analysis was by pooled odds ratios from individual studies in order to use random effects model. Analysis was performed using Revman 5.3 statistical software. Relative risks with 95% confidence intervals from each study were combined for meta-analysis using the Mantel-Haenszel method. Data was combined from observational studies and used the random-effect model assuming that studies estimated the same treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods were assessed sufficiently similar. Heterogeneity effects were assessed graphically using forest plots and statistically using chi-squared and I^2 test.

3.5 Results

The initial search performed in 2012 revealed 351 publications from 3 databases (MEDLINE 128, EMBASE 215 and CINHAL 8) with 87 duplicates which were excluded leaving 264 references. This search was performed as a part of preparation for COTS trial and application for HTA grant. Before submission of this thesis the search was repeated and extended from March 2012 to November 2016. A further 123 publications from 3 databases were identified (MEDLINE 34, EMBASE 83 and CINHAL 6) with 32 duplicates which were excluded leaving 91 references to be included into systematic review. There were no randomised controlled trials identified. So overall 474 publications were identified. From them 119 duplicates were removed and the remaining 355 manuscripts abstracts were revised. From the title and abstract, 302 studies were excluded as it was clear that they did not fulfil the selection criteria. Full manuscripts were obtained for the remaining 53 articles: from these 49 studies were excluded. Therefore, 4 studies reached the inclusion criteria. There were insufficient data available on 2 of them and after contacting authors it was excluded from the review leaving 2 papers. When we have assessed them using Newcastle-

Ottawa scale, they had low risk for bias and were included into meta-analysis. Figure 12 demonstrates the study selection.

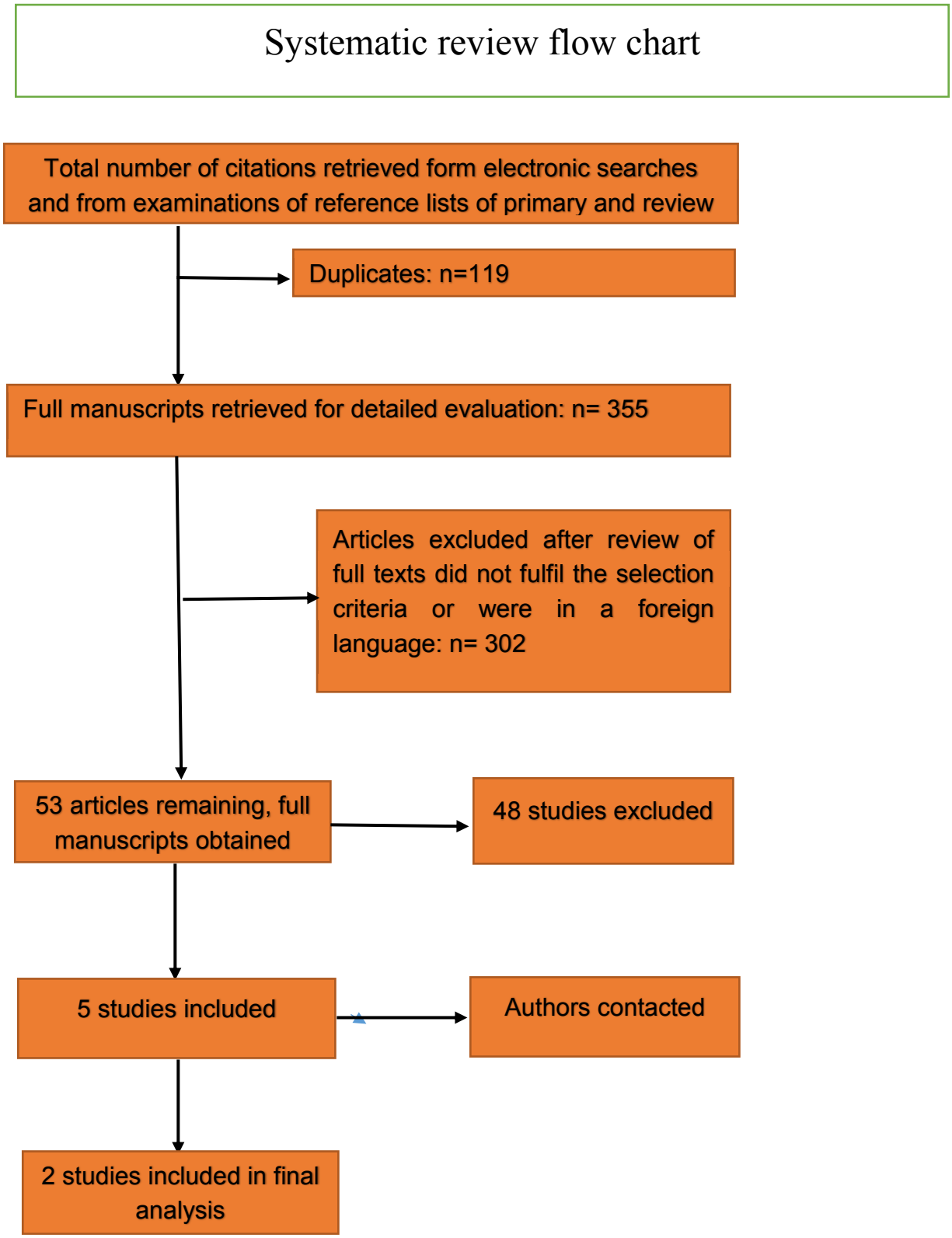
First one, by Kindinger et al[116], is of a retrospective nature, which undermines its quality but on the other hand the sample size is large and covers few centres in UK. This study also includes a prospective cohort but patient was only followed up until 16 weeks of pregnancy in two different cohorts (multifilament versus monofilament). The outcomes of pregnancy in prospective cohort are not presented. The retrospective review though includes data from large UK centres (including data from our retrospective analysis) and outcomes for preterm birth rate were similar in each of them. The authors give all the details of cerclage insertion such as gestation at insertion, indication for cerclage, suture material used and outcomes of PTB and nonviable birth. They also specify metadata such as age, parity and previous obstetrical experience of the included patients. They present clear statistical evidence of favourability of monofilament material over multifilament comparing rates of pregnancy loss in both cohorts of patients (15% versus 5%, respectively; with $P<0.0001$). Apart from pregnancy loss they present rates of PTB which is again higher in patients who received braided suture cerclage (28% versus 17% respectively; $P<0.0001$).

The second paper, by Shoenfield et al is poorly controlled. Even though it is a randomised trial, the authors did not specify what kind of randomisation was used, the numbers were small (10 in each arm only). The patient selection criteria were not very clear with single specification that randomised patients had proof of cervical incompetence. The exact inclusion and exclusion criteria are not given. The authors also declared that they evaluated suture materials used for cerclage. Their conclusions were based on post-procedure complications and pregnancy outcome. The main limitation of the study is that neither those complications nor pregnancy loss itself are specified. The pregnancy loss, which is a primary

outcome, is not specified in details whether it is midtrimester miscarriage or intrauterine death or neonatal death. They also did not give any data on gestation of insertion or removal or gestation at which pregnancy loss has happened. A further limitation was absence of any data on neonatal outcome, admission to the neonatal unit, short or long term follow up.

On another hand, they described in detail the methods of investigations used for suture material used in cerclage such as (scanning electron microscopy (SEM) with the use of cathodoluminescence and X-ray diffraction analysis). They also investigated the sutures before and after insertion (on removal). Both methods proved that monofilament suture didn't change in structure and its surface remained unaffected. Alternatively, SEM method proven that multifilament tape was covered with specific "coating" which consisted of mucoproteins and phagocytes and X-ray analysis found significant changes in structural degradation of the fibres of the tape after use. The authors link presence of coating to infection rate in 4 out of 10 patients who had cervical cerclage with braided tape. They demonstrated that the monofilament suture didn't have such a cover after use and as result had a better outcome, such as there were no pregnancy loss in 10 patients who had the monofilament cerclage. Again the quality of the outcome was poor as it did not specify the gestation at which patients delivered, mode of delivery and neonatal data.

Figure 12 Study selection process for systematic review of type of suture material used in planned/elective vaginal cervical cerclage



	Case-cohort representative	Selection of non-exposed control	Assessment of exposure	Outcome negative at start	Comparability by design	Comparability by analysis	Outcome assessment	Duration or follow-up	Score
Kindinger et al (2016)		*	*	*	**	*	*	*	9
Shoenfield et al (1999)	*	*	*	*	*	-	*	*	7

Table 5 Appraisal of methodological quality by Newcastle Ottawa Scale

*- Indicates that feature is present; - indicates that feature is absent. For comparability by design this checklist awards a maximum of 2 stars (**) and (*) or none if the feature is completely absent.

3.5.1 Study characteristics

Two studies included a total of 691 women. The study characteristics including sample population, number of women, type of cerclage and outcome of pregnancy presented in table 6.

Table 6. Study characteristics

Author, year	Sample population	Patient number	Study design	Outcomes measure
Shoenfeld et al 1999	Women with cervical incompetence	20	Randomised, type of randomisation not specified	Pregnancy loss
Kindinger et al 2016	Women receiving planned cervical cerclage	671	Retrospective cohort study	Non-viable births (delivery before 24/40 or intrauterine death)

It is worth mentioning about studies which we didn't include in analysis. First one looked at type of suture material used in ultrasound-indicated cerclage but compared two types of braided sutures Mersilene or Ethibond to Mersilene tape[96]. As a result, the findings could not be included in the review as our research question was about comparing braided versus

monofilament sutures. We still contacted the author to clarify whether they had any data on Monofilament suture use in ultrasound-indicated cerclages. The response was that they only used braided material such as Mersilene suture and Mersilene tape. The second author Abdelhak YE et al [95]compared absorbable and non-absorbable sutures for cervical cerclage. Again we wanted to be specific whether sutures were braided or monofilament. There are some monofilament sutures like Nylon for example which are not absorbable. It was impossible to contact the author. So as a result only two studies were included into analysis.

3.5.2 Quality assessment

The Newcastle-Ottawa scales for Quality Assessment are presented in Table 5. The studies scored well on both scales. We were unable to create a funnel plot as only two studies were included in analysis so not possible to assess asymmetry.

Figure 13 Meta-analysis of studies of type of suture material used for cervical cerclage

3.6 Discussion

This meta-analysis included 2 studies including 691 women. It found that the type of suture material appears to influence the outcome of pregnancy with planned cervical cerclage. Use of multifilament braided sutures is associated with higher pregnancy loss.

This review was strengthened by methodology. I used an extensive search strategy and used valid data synthesis methods. I used the Newcastle-Ottawa quality assessment scale for NRS studies. They scored well on the scale suggesting low risk of bias. Furthermore, no language restrictions were applied. The first study is relatively large (n=671) covering five big obstetrical units in UK with similar rates at each unit both for PTB and non-viable birth. They present data on both types of suture material and prove statistically that stich used in cerclage was the major variable which had impact on the risk of PTB independent of other variables such as maternal age, ethnicity, parity, and history of a previous PTB. They link poor outcome for pregnancies where braided sutures were used for cerclage with promotion of vaginal dysbiosis which leads to tissue inflammation and cervical remodeling due to that. The second study, even though small in size (n=20), gives very detailed information on suture material used in cerclage which was examined by special methods (SEM and X-ray diffraction analysis) and proves that monofilament material is associated with low rate of infection and had better pregnancy outcomes.

The review is limited by the number of included studies being only 2. Both studies have limitations. The first study by Kindinger et al is a retrospective review and there is no doubt that studies which do not involve randomisation are liable to potential bias. Even though it includes the prospective cohort, the outcomes are not presented. The second study is randomised but, as mentioned previously, authors do not specify type of randomisation. This

study was poorly designed not presenting important data on gestation at suture insertion or delivery, mode of delivery, demographic or any neonatal data.

This systematic review addressed a research question, which could potentially save lives of more than 400 babies per year in UK dying as a result of mid-trimester loss, intrauterine infection or complications of prematurity. Moreover, reducing the risk of prematurity will reduce neonatal unit and hospital stay, the significant morbidity associated with early gestation and the associated long-term morbidity. This will have psychosocial benefits and significant cost saving for the NHS and the wider community.

So in conclusion, this systematic review and meta-analysis demonstrates grade 2 evidence of a statistically significant difference in pregnancy loss associated with type of suture material used. It relies on evidence from very small NRS and studies which do not involve randomisation are potentially at higher risk of bias and overoptimistic results. So there is a need for proper RCT to address this issue. This study has commenced recently and is recruiting in the UK (C-STICH trial). The analysis of the data has resulted in a study requiring 900 to be randomised and at the time of writing had recruited around 350.

Chapter 4- National survey

4.1 Types of survey

4.1.1 Background to survey methodologies

A survey is a tool that can be used in qualitative research. It is a method of gathering standardised information from a sample or cohort of individuals. One of the uses of such surveys is to collect information in order to investigate whether current opinion, attitude or existing facts should be challenged[121]. Various methods can be employed to conduct a survey; examples of delivery mediums include postal, on-line, street, in-home, telephone, fax and interview. Each of these methods has advantages and disadvantages and has certain characteristics to other methods in common. The use of such surveys has a place in medicine as they can give the opportunity to healthcare professionals to collect systematic information on numerous factors such as the aetiology of the diseases, incidence of certain conditions, quality of life, etc. Despite this, according to some authors, this tool is unfortunately not widely used by medics[122]. There are factors which will influence the clinician's choice regarding the type of the survey to be carried out including required amount of data, sample size, time frames for completion of the project, accuracy of responses and avoidance of bias, cost of the survey and levels of non-response[123].

4.1.1.2 Postal survey

Postal surveys for example, involve the costs for postage, supply and individual's time. Response time relies on the existing postal system. Data collection requires manpower. Postal surveys are widely used in educational enquiries[124]. Hoinville and Jowell in 1978 identified some important factors that can influence the success of postal survey. Among them was using quality envelopes with the typed name of addressee. A second factor was

to use first class service with enclosed first class envelope for response[125]. The day of the week for mailing also seemed to be important. For example, if a postal survey was used for organisations then Monday and Tuesday were recommended. For personal surveys, Thursday was the best day for mailing out. They also recommended sending a follow up letter which was shown to maximise the response significantly. Follow up letters should re-emphasise the importance of the survey and contain a further copy of the questionnaire with a first class envelope for return. The number of follow up letters obviously is limited but it can increase the response from 40% in a well-planned postal survey up to 70-80% with reminders used. Follow up letters should be sent 3 weeks after initial contact. If a second follow up is planned then the recommendation is a one-week gap. Follow up can be telephone as well as by post. Apart from follow up letters, the use of incentives is recommended in order to maximise response, especially when used with the first mailing. They should be selected accordingly and not perceived as a payment for efforts. Use of neutral incentives is recommended, for example stamps, or cheap pens that can be used to fill the questionnaire. According to the authors, these initiatives can create a sense of obligation to complete the questionnaire in the postal survey participant. Hoinville and Jowell developed a special flow chart for researchers who would wish to conduct a postal survey that can simplify the process. The flow chart presents different stages of the survey and the recommended sequence of it.[125]

Whilst the response rate of a postal questionnaire is important, the investigators must also address the question of validity. Belson (1986) addressed the issue of the validity of the postal questionnaire by trying to identify whether respondents who completed survey answered questions accurately and whether those who failed to respond would have given the same answers as responders[126]. He offered a twelve step approach to be used in order

to check the accuracy of the postal survey, including familiarisation, probing, and challenging. He also suggested following up non-respondents by means of interviews and then comparing answers with respondents in order to address the issue of 'volunteer bias'. Once data is collected it has to be cleaned and made suitable for analysis. For example, data is coded by hand for small surveys or with the help of computers if it consists of large data. Questionnaires are edited prior to coding. Editing eliminates errors. This process involves performing checks on *completeness* and accuracy i.e. that every question is both answered and answered accurately. Missing answers can be followed up by contacting respondents again or by checking other parts of the survey. With regards to accuracy, sometimes the wrong box can be ticked or the wrong code is applied which can lead to errors unless data is edited. It is also important that interviewers, those who are editing postal survey responses, are doing so uniformly following clear instructions. This *uniformity* leads to eradication of errors. Coding is important for subsequent computer analysis but not all data can be reduced for this purpose[124]. Sometimes coding can be included into the questionnaire itself, so answers are going to be pre-coded. When coding is done after a postal survey is completed and the questionnaire is answered, then it is called post-coding. Pre-coding can be used for close-ended questions, for example male/female, single/married/divorced. For open-ended questions, special coding frames are developed once a questionnaire is developed. For example, a random sample of questionnaires is taken and "a frequency tally of the range of responses as preliminary to coding classification". Once a frame is developed the next step is to check validity.

4.1.1.3 Fax survey

Another type of survey is a fax survey. Fax surveys are not popular as they involve the presence of machines on both ends (receiving and sending). On the other hand, telephone surveys/interviews are quite popular especially when the time to conduct a survey is limited. Telephone surveys can be limited to certain times of the day as people may not be able to answer the phone while they are at work, so calling time is limited to certain periods. In general, people may be reluctant to answer phone interview calls and would block certain numbers.

4.1.1.5 In-person surveys

In-person or face-to-face interviews tend to be expensive and quite often are conducted when more complex data needs to be collected[127] and with a smaller proportion of the population (e.g. elections) or with a smaller sample size. They are widely used in qualitative research[128] and classified according to the degree of structure and directness. The interviewer has a freedom to structure the questionnaire applicable to each conducted interview. Directness – is awareness of the survey participant of the survey's purpose. In face-to-face interviews errors can be easily introduced first of all by misinterpretation of replies given by the participant to the interviewer. The attitudinal questions cause significant variance but they can't be predicted easily[129]. Surprisingly the success of the in-person interviews doesn't depend on interpersonal skills and personality of the interviewer[130]. Telephone interviews is a sub-type of in-person interview. They are cheaper to conduct, quick and effective method of survey especially when trained personnel is used.

4.1.1.6 Web based survey

With the advent of the internet, web based surveys have emerged which require access to the Internet on the sending and receiving end[131]. Web based surveys may be password protected and responses are collected and collated immediately into a pre-created

database[131]. Some studies have shown that several hundred responses can be generated within a short time frame using this method[132]. The advantage of this method is that information on response is available imminently, with specific information on how many questions were answered and how much time were spent on each of them. Web based surveys are usually not expensive to conduct as implementation is free and there is no cost for postage or paper. There is only a cost of designing the web page. Data analysis is simple as it is directly connected to analysing software[132]. The data is considered to be more "clean" as responses are entered directly by the participants thus excluding biases from survey conductors. Limitations include participants needing an email address and access to the Internet.

Web-page based surveys usually cover large groups of users while email-based surveys cover small homogenous groups[132]. Advantages include participants being able to remain anonymous, if they wish, with the support of encryption technology, otherwise their names and email addresses may have to be collected automatically through email response. It has been shown that lack of anonymity does not decrease response rate[133]. Email based surveys allows the researcher to create a list of non-responders and re-request participation in the survey by sending reminders. That increases the overall response rate. An advantage of email surveys over the postal survey is that any duplicate responses where the researchers sent numerous multiple questionnaires in an attempt to increase response rate can be eliminated[134]. Emails may contain survey questions, attachments or include a hyperlink for the website where questions would appear in a chronological order

5.1.2 Steps of successful survey

Overall the following factors are considered key to the success of any survey, irrespective of type:

1. Addressing ethical issues.
2. A well-designed/formulated questionnaire.
3. Identification of target group and selection of sample size.
4. Piloting the questionnaire.
5. Data collection and analysis of pilot data with implementation of any required changes.

Conducting surveys necessarily involves an element of intrusion into the subject completing the questionnaires life. Consequently there is potentially an ethical issue- of invasion of privacy.[124] Survey respondents cannot be forced to complete the survey and the following rights apply: 1) right of informed consent; 2) right to withdraw from survey at any stage or answer only on certain questions; 3) guarantee of confidentiality and anonymity, unless expressly waived, which will normally reduce non-response rate but has been questioned by many qualitative researches[135, 136]; and 4) non-maleficence, meaning that participation in research/survey can harm them[124].

The second important issue is survey design which plays an important role in response rate. Questionnaires should be simple and short. For web and email surveys having a welcoming note, clarifying who you are and why you are doing the survey is beneficial. The quality of this message will encourage people to complete the survey. If options such as “Don’t want to answer”, “Don’t know”, “Not interested”, “Not applicable” are not included then some of the respondents may not even consider answering the question as they would feel forced into giving an answer. It is a good idea to leave space for comments at the end as one can

pick up interesting thoughts, views, and opinions which were not covered by survey questions but which may be important for the topic of the survey.

Sellitz and her group have published a guide to help researchers formulate and construct their questionnaires[137]. There is a staged sequence for planning a questionnaire. First of all, one needs to decide on the purpose it is going to serve, to identify the targeted population and to define the sample size. Moreover, it is important to identify issues to be addressed and to select the kinds of scales/measures/questions that are required. Piloting a questionnaire is always a good start before implementing the final version.

The phrasing of the question and language used is important when developing a questionnaire. It is critical that surveyors and respondents have internal consistency and validity so that they assign the same meaning to the words used in the questionnaire[128], for example when surveyors, medics and respondents are patients. Questionnaires can be structured, semi-structured and unstructured. They can contain closed and opened questions, multiple choice, rank ordering, ratio data questions, constant sum questions, rating scales and dichotomous questions. Irrespective of question type, collected data can be very accurate[128] with open-ended questions being the most difficult for analysis. The advantage of open-ended questions is that respondents have a chance to disclose their own beliefs and views, which are normally linked together and explored as themes. The best reliability and reproducibility is with dichotomous questions (yes/no answer) especially when collecting information about the health matters[138] but some authors[139] think that they can lead to significant bias as usually people have a tendency to agree with the statement rather than disagree. The designer of the questionnaire has to decide not only on the type of questions to be used but also on scales of data to choose.

One of the most important parts of any survey is identification of the targeted population or “sample”. A decision on the sample size can be defined by various factors. For example, the statistical quality needed for findings, also on financial and human resources available to conduct the survey. The “sample” should be representative of the target audience and have characteristics of the total population[127]. One should be careful to avoid a biased sample as it may skew the end results. It is a well-known practice for large companies to create a separate research company to conduct their surveys to avoid potential bias as people may be more open to the third party[140].

Once a questionnaire is prepared and the targeted group identified piloting can take place. A pilot performs several important roles. It increases reliability, practicability and validity of the questionnaire[141]. For example, it is aimed to:

1) Gain feedback on questions.

2) To test time taken to complete questionnaire.

3) To identify irrelevant questions.

4) To identify misunderstood or non-completed items.

5) To test whether questionnaire is too long or too short.

6) To get feedback on layout and numbering etc.

There are two types of piloting. First one described above will concentrate on format of questionnaire and is not focused on data. It is distributed to limited number of respondents to gain their feedback. The second type will include a long list of questions which are eradicated through statistical analysis and feedback[142]. The data gained through the pilot will be analysed for reliability, collinearity, multiple regression and factor analysis. So through

this statistical analysis data will be removed and result in a shorter questionnaire of smaller proportion. The number of respondents in these circumstances has to be significant in order to generate reliable data for statistical analysis.

The results of a survey can be presented in departmental meetings, emailed to stakeholders or published in the press, journals or books depending on reasons for the survey being conducted.

4.2 Aims of the survey used in this thesis

To conduct a survey to review practice amongst UK based obstetricians with regards to cervical cerclage procedure to understand current practice in the UK. A specific aim was to inform the researches about what emphasis the respondents attached to the suture material type used during surgery and its potential impact on outcomes and to inform on a subsequent trial design.

4.3 Methods

There are several advantages of internet-based survey which made this tool more attractive to me and as a result I have implemented it in order to perform my survey. As COTS was unfunded, cost played a major role. Internet-based survey significantly reduces the cost as there is no postage, printing or interview expenses involved. I also decided that this method will be the quickest as there is no time wasted to distribute, collect and analyse the data. All data will be entered into the web-based survey and processed automatically. Implementation of internet based surveys is often quicker due to the availability of survey templates. Internet-based surveys can also be distributed more quickly to a larger number

of participants compared with other survey methods. The participants can access and complete the survey in a time-frame to suit them in a self-chosen setting, for example at home or at work. The errors can be highlighted to the participant immediately thus giving the opportunity for correction resulting in less missing entries than in paper based surveys.

Taking into considerations all mentioned advantages and based on the methodologies described above, I developed a pre-test questionnaire. This was piloted within a group of independent consultants at Birmingham Women's Hospital before being modified and the final questionnaire being used to carry out a national survey. The aim of the pilot was to identify any areas for improvement such as wording, and length, as well as any unanticipated issues. A questionnaire was designed with the support of Birmingham Clinical Trials Unit (BCTU).

Results of the pre-test questionnaire were analysed by members of the survey team and all applicable suggestions on modification of questions, their structure and sequence, were incorporated into the last version of the questionnaire. There were only few modifications such as adding one more primary outcome to question 9 (preterm birth rate less than 34 weeks) and the sequence of questions were changed putting all questions about cerclage practice first followed by questions about the research proposal.

The Royal College of Obstetricians and Gynaecologists maintain a list of UK based members and fellows who are Consultants obstetricians and gynaecologists who have agreed to participate in surveys. This list can be accessed through an application to the college giving details of the survey and reasons for wanting to circulate it (see request form attached **- Appendix 2**). Our application was successful with no modifications. There was no delay in response from the RCOG thus we could initiate our survey in timely manner.

Ideally we would have liked to be able to identify Consultants who no longer practices Obstetrics so as to be able to exclude them from the survey distribution and our denominator but this information was not on the RCOG register [121]. We were able to exclude known Gynaecological Oncologists as they were unlikely to carry out obstetric procedures. Members and fellows were contacted via the email address listed on the RCOG database for them. A link to the survey with an introduction explaining the purpose of the survey was sent. Selected members and fellows were sent an invitation to complete an electronic survey via the Survey Monkey@ platform. This survey was conducted between February and April 2012 with single reminder six weeks after the survey launch. There were several reasons why we decided to use Survey Monkey as a web based on-line survey tool. Firstly, BCTU had a significant experience in conducting survey through Survey Monkey platform and recommended it. It is free and therefore did not use any of the limited resources available for this thesis. It could be customised to our needs so that the programme not only collected the data but also performed data analysis and bias elimination. There were also significant ethical advantages as well in that responder IP (Internet Protocol) addresses are not collected, enabling respondents to remain anonymous.

4.4 Results

A total 1334 members and fellows were sent a link via email and 261 (19.5%) completed the survey. The denominator for each question was different depending on the number of respondents per each question [121].

The main objectives of the survey were to identify current practice of Consultants and Obstetricians related to elective cervical cerclage. These included criteria for patient selection for elective cerclage; types of cerclage technique used; gestation at insertion;

number of cerclages performed per annum; and existence of local protocol or guideline to support their practice. The list of questions within the survey is shown in Table 7.

Table 7. Survey questions

Q1. Do you ever perform elective cerclage to prevent midterm pregnancy loss and preterm birth? 1. No, I never perform elective cerclage as I do not see women at risk 2. No, I never perform elective cerclage even though I see woman at risk 3. Yes, I perform elective cerclage
Q2. I perform cerclage on the basis of 1. History of 2 or more midtrimester losses or preterm deliveries < 28 weeks 2. Cervical sutures in previous pregnancies 3. History of cervical surgery (e.g large cone excision) 4. Risk of shortened cervix (<25 mm) 5. Other
Q3. Which approach do you predominantly use? 1.Transvaginal cerclage (McDonald) 2. High transvaginal cerclage (Shirodkar)
Q4. Do you use Multifilament (e.g. Mersilene) or Monofilament (e.g. Nylon) sutures for elective cervical cerclage? 1.Multifilament 2. Monofilament
Q5. At what gestation do you usually/prefer to insert your elective cervical sutures?

1.Pre-pregnancy

2.<11 weeks

3.12-16 weeks

4.>16 weeks

5. other (please specify)

Q6. Do you have a guideline for insertion of cerclage in your department?

1.Yes

2. No

Q7. How many elective cerclages do you estimate are done annually in your Unit?

1.0-20

2.20-40

3.40-60

4.>60

Q8. Do you consider multifilament vs. monofilament an important research question?

1. Yes
2. No
3. Not sure. Please send me information

Q9. In your opinion, what is the outcome that will change your practice (rank the importance from 1 (most)- 8 (least)?

1.Pregnancy loss before 24 weeks

2.Gestation at birth

3.Live birth rate

4.Preterm birth before 34 weeks

5.Take home baby rate

Q10. Do you have any more comments

Table 8 Number of responses for each proposed primary outcome by rank.

Answer options	1	2	3	4	5	6	7	8	Total response count
Pregnancy loss<24 weeks	66	29	15	18	29	6	1	11	175
Gestation at delivery	54	42	41	15	14	6	6	1	179
Live birth rate	21	43	27	35	19	13	9	7	174
Preterm birth rate<34 weeks	27	36	45	30	21	7	3	3	172
Take home baby rate	66	31	24	18	9	9	7	8	172

4.4.1 Current practice with planned cervical cerclage procedure

The main objectives of the survey were to identify current practice of Consultants Obstetricians related to elective cervical cerclage. These included criteria for patient selection for elective cerclage; types of cerclage technique used; gestation at insertion;

number of cerclages performed per annum; and existence of local protocol or guideline to support their practice.

Consultants were questioned whether they perform planned cervical cerclage in their routine obstetric practice in order to prevent SMTL or PTB and if they do is the inclusion criteria for cerclage based on RCOG No.60 guideline[64] (at the time the only guidance available for cerclage practice which is currently archived and replaced by NICE guideline on preterm labour and birth[14]).

The majority of consultants (88%; n=227/258) performed a planned suture insertion in their routine practice. There were two reasons for not performing planned cerclage. First, obstetricians (5%; n=13/258) who would not offer cerclage as a treatment option for women with a history of PTB or SMTL. Second 7%(n=18/258) of obstetricians who would not perform cerclage as they were not involved in provision of care for this group of patients.

Of the 202 respondents 77.2% (n=156) do less than 20 cerclage procedures, 19.3 %(39) perform between 20 and 40, 4 (2%) perform between 40 and 60 and only 3 (1.5%) perform more than 60 cerclages per annum respectively.

Fifty of 200 respondents confirmed that they follow their hospital guideline on cervical cerclage. The majority, though, follow the RCOG recommendations for cerclage insertion.

Of the 202 consultants addressing the question on indications for cervical cerclage, 75.2% (n=152/202) insert cerclage if there is a history of two or more mid-trimester losses or preterm deliveries in the past. 72.8% (n=147/202) will consider cerclage if the patient had it in a previous pregnancy. 54.5% (n=110/202) will insert suture on the basis of shortening of the cervix on transvaginal scan<25 mm.

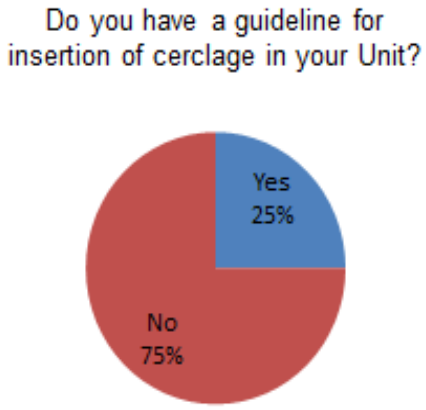


Figure 14. Availability of cerclage guideline in units

We were also interested in whether Consultants would offer cerclage to women with history of cervical sutures in previous pregnancies, as we were unsure as to how commonly this was still accepted practice, or any other personal criteria or hospital guideline.

For each question of the survey, there was a possibility of leaving appropriate comments. Comments added in this section illustrate a lack of clear guidance as when to offer the cerclage:

"We need to know if cervical surveillance should be done with after a single LLETZ as some patients insist".

"We insert very few elective sutures, most on women who have been referred to a specialist".

"Pre-term labour clinic due to identification of risk factors and are identified with signs of cervical shortening between 16-20 weeks. Truly elective cerclage tends to be performed on women who have had this in previous pregnancies and wish to have this repeated rather than monitor the cervix for signs of incompetence".

"Preterm reduction is by 46% and 40% respectively for progesterone treatment and cervical cerclage. There is no different on both treatments. With the surgical risk associated with cerclage more and more women now select progesterone treatment".

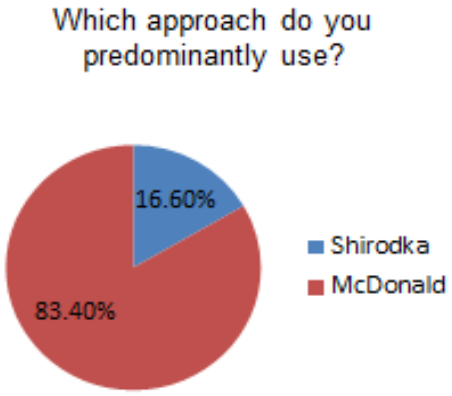


Figure 15. Type of cerclage used

The questionnaire also included items on approach for cerclage, type of technique, vaginal (McDonald) or high vaginal (Shirodkar), and type of suture material used: Multifilament or Monofilament. Preferable gestation for suture insertion was one of other questions to address. The majority of respondents (88.7%; n=180/203) stated that they perform procedure between twelve and sixteen weeks of gestation. With regards to the technique used McDonald type of cerclage remains the most popular among obstetricians (83.4%; n=166/199). The Shirodkar technique is less popular with only (16.6% n=33/199) reported using it.

Comments accompanying this question highlighted significant variation in cerclage approach and were as following:

"The type of cerclage I put in depends on the length of the cervix at the time of insertion – if the cervix is a good length then McDonald, if not then I dissect the bladder off like the beginning of a vaginal hysterectomy and go as high as I can".

"Technique is important to get high with the posterior bites so that weight of the pregnancy is not transmitted the suture".

"Performing a Shirodkar needs a wider tape or heavier duty Nylon, but how many people can perform a true Shirodkar any more, will this be a biased trial anyway …"

"I see no place for a Shirodkar style suture. If there is not enough infra-vaginal cervix to insert a high cervical suture, then an abdominal is required, hence the bladder is not touched".

"Choose my method of suture according to history and clinical findings".

4.4.2 Type of suture material used for cerclage is an important research question

One of the most important questions for us was the type of suture material practitioners' use for cerclage insertion and whether they think that the research question of impact of type of suture material on the outcome of cerclage is an important question to address.

Most of the respondents routinely used multifilament braided sutures (86.6%; n=175/202) and (16.6%; n=33/202) monofilament.

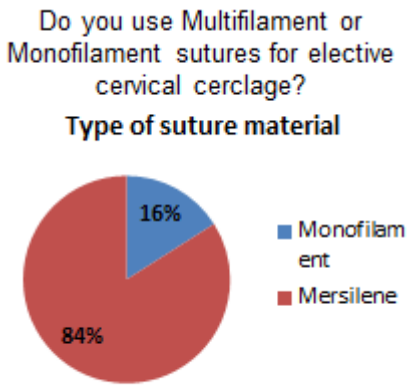


Figure 16. Type of suture material used for cerclage

Almost half of the respondents (47%; n=94/201) considered the question of type of suture material used in cerclage comparing multifilament braided versus monofilament suture an important research question. A further (27.9%; n=56/201) were not sure and commented that would want to receive more information.

The following quotes illustrate the lack of information about Monofilament suture use in cerclage:

"It is a traditional practice to use Mersilene in our unit. PDS is used in our unit by some Obstetricians for rescue cerclage".

"I was not aware that McDonald can be done using monofilament sutures. If McDonald is

done using monofilament sutures, it would be interesting to share information with Obstetricians who have the widest experience".

"I have seen quite a number of the Nylon sutures cut through the tissues. Success is all to do with identifying the correct patients, placement of the sutures appropriately and timing of insertion".

"Mersilene seems to work fine and we don't have urogynae type complications due to short duration of use. Infection may be a factor and would make us change practice. SROM?"

"I have come across several women with embedded monofilament material from previous cervical suture? PDS inserted abroad - I have never seen anyone use other than Mersilene in UK. I think there may be a concern that finer suture may cut through more easily".

4.4.3 Important primary outcome for future studies

This survey was conducted as part of the justification to undertake COTS as a pilot/feasibility study. At this point in time our team of researchers were still equivocal about our primary outcome and hence the rationale for question 9. We therefore asked consultants to grade a list of possible outcomes on an 8-point scale where 1(most important) and 8 (least important)[121].

The sequence of rating was following:

1) The most highly rated outcome-gestation at delivery.

2) "Take home baby rate".

3) Pregnancy loss before 24 weeks of gestation.

4) Preterm birth before 34 weeks of gestation.

5) Live birth rate.

Comments expressed by some consultants regarding primary outcome that can change practice included:

"*To me, the woman's desire is to take a baby home. I feel that should govern our practice. Would be interested in your multi versus mono filament question!*

"Take home baby rate has been considered in some meta-analysis and has to be the most important factor- but also consider take well home baby rate. We sometimes manage to get a woman to 24 weeks but the baby has severe problems."

4.5 Discussion

Obstetric practice for inserting cervical cerclage has remained unchallenged and controversial since the MRC study[65]. In the mid 90's, the issue of cervical length was thought to be the key to improving selection to get better results from more selective cerclage. Until now, the issue of the impact of material type had not been addressed. This national survey was the first attempt to assess current practice with regards to elective cerclage procedure among UK consultant obstetricians and gynaecologists and to identify their views on our research hypothesis of whether the type of suture material can influence the outcome of planned cervical cerclage. The information obtained from the survey revealed major variations in some aspects of cervical cerclage practice, especially to the type of suture material used in cerclage. It also confirmed that many obstetricians are " in equipoise with regards to the best suture material for cerclage"[121] and that they were willing to participate in the study to address this question. The survey also identified a number of opinions and attitudes which were incorporated into research protocol for the COTS feasibility study,

evaluating the impact of suture material on the outcome of pregnancy following cervical cerclage comparing multifilament/braided sutures to non-braided monofilament.

At this point in time there was no power calculation to know whether it was representative and the list was derived from self-selected consultants who were willing to be contacted. Our response rate was 19.5% and was comparable to the average response rate for RCOG conducted surveys, which is 20%. This therefore suggests our survey performed consistently when compared to other RCOG surveys. Most of the RCOG facilitated surveys faced the same issues as we did and that is probably the reason for the presumably low response rate[143, 144].

There are several factors, which could have influenced the response rate of any e-mail survey and ours in particular. The most common problem while conducting surveys is to obtain a sample frame in which every individual in the selected population has a known chance of being selected for participation[126]. We believe that had significant impact on the response rate of our survey. We were only able to contact those Obstetricians, who were happy for RCOG to disclose their contact details for survey purposes. Also, from 1334 contacted some were practicing Gynaecology or practicing Obstetrics but not performing cerclage procedure, so were unable to participate in the survey. As a result, there was a decreased sample size, and we will have missed all the numerous Consultants who regularly perform cerclage and could have provided a valuable opinion on existing issue. So, we could have possibly obtained a higher response rate if we had avoided those issues. Having said that there is a good chance that the themes would have reached saturation by 200+. With this in mind we were reassured that the survey was well received and that the information obtained was representative and provided all the information to guide in the study design. So whilst we could have potentially obtained a higher response rate we believe that it was

unlikely that it would have given any greater granularity to the information obtained and we believe that the sample of consultants who participated, can still be considered representative of the larger group of obstetricians involved in provision of cerclage services. We could have also contacted BMFMS (British Maternal and Fetal Medicine Society) or preterm prevention clinics in tertiary hospitals to get the opinion of Consultants directly involved in cerclage provision but limitation in time didn't make this possible.

The results of this survey confirmed significant variation in practice[121]. We were able to establish that consultant Obstetricians were keen to participate in a research study looking at the type of suture material used for cerclage as most (75%) were still in equipoise regarding this matter. Considering there are no existing recommendations on the type of suture material to be used for cerclage, 86% of Mersilene use is extremely homogenous. On the other hand, some of the Obstetricians (according to comments left) were not aware about potential complications, associated with braided non-absorbable sutures such as erosion and infection, which are seen in other disciplines using multifilament meshes/tapes/sutures. As a consequence, there has been little to challenge this practice and explains why many still prefer to use Mersilene for its perceived strength. It is also easy to remove which is almost certainly due to its encapsulation[103] and some of the practitioners are not aware and have never been taught that there is a possibility of using Monofilament sutures such as Nylon or Prolene for cervical cerclage.

From the results of the survey, it is quite obvious that there is little consensus on the guidance as to when to offer cerclage and which category of patients would benefit. Most of the respondents loosely follow criteria suggested by RCOG guideline[64] but, at the same time, there are practitioners who would offer cerclage based on their individual personal preferences.

The RCOG Guideline recommendation was to offer history-indicated cervical cerclage to women with a history of 3 or more mid-trimester losses and/or preterm deliveries <28 weeks; not to routinely offer it to women with a history of two or fewer mid-trimester losses or preterm births. The guideline also stated that cerclage can be offered in a planned manner to women with a shortened cervix on transvaginal ultrasound scan (less than 25 mm) who have a history of mid-trimester loss or preterm birth in the past and are less than 24 weeks of gestation. It did not suggest cerclage just only in case there is funnelling of the cervix without shortening. Women with an incidental finding of a short cervix on the scan should not be offered planned cerclage procedure, based on evidence from a randomised controlled trial of 302 women with singleton pregnancies and history of preterm birth or mid-trimester loss who were offered cervical length measurement versus expectant management. Insertion of cervical suture reduced the rates of both perinatal death and pre-viable birth but did not show an impact on the rate of preterm birth before 35 weeks of gestation; which was only significant if the cervical length was less than 15 mm[91]. A meta-analysis of 607 pregnancies confirmed that insertion of cerclage in women with short cervixes (less than 25 mm) and the same inclusion criteria led to reduction in delivery before 35 weeks of gestation[75].

The current guideline does not specify planned cervical cerclage as a procedure, instead it divides cerclage into 3 categories of history indicated, ultrasound indicated and rescue. In our survey we were only interested in the first two of these indications as such. That is why we defined it as planned cerclage (combining history indicated and ultrasound indicated) which are performed electively.

Only a quarter of respondents had a hospital/departmental guideline to follow. The issue of patient selection will influence reported success rates of any surgical procedures. The significant variation in a patient's selection and the indication for cerclage has been

attributed to variation in reported success rate for the procedure. According to our survey the majority of respondents had a variation in the RCOG guideline in that they would offer a planned cerclage to the patients who had a history of previous two or more mid-trimester losses or preterm deliveries and would offer that between 12 and 16 weeks of gestation (88.7%). Again there was significant variation from the RCOG guideline in women with singleton pregnancies and a history of previous cervical surgery such as large loop excision of the transformation zone, cone biopsy or any destructive procedures on the cervix. This stance is supported by recent evidence that large loop excision of the transformation zone is associated with an increased risk of spontaneous preterm birth[145] . For those women it may be the only treatment option available especially now that the OPPTIMUM trial has confirmed that vaginal progesterone does not prevent preterm birth in women at risk of preterm delivery before 34 weeks of gestation[60].

Our survey also suggested that on average most consultants perform less than 20 cerclage procedures per year. Taking into consideration the context of recent recommendations from NICE/RCOG regarding the annual workload for other surgical procedures, one could argue that in order to maintain the competence in the cerclage procedure, practitioners need to perform a certain number of them per year. For example, NICE recommends that in order to keep competence in urinary stress incontinence procedures, surgeons should perform at least 20 of them per year[146]. The RCOG on the other hand, recommends to do least 30 invasive procedures annually in order to keep competence in amniocentesis[147] .Given that there is evidence to confirm that, surgical competence is related to the outcome of the procedure, and that the benchmark is set for fetal medicine and urogynaecological procedures, there is an argument that there probably should be one set for cerclage as well[121].

One of the most important outcomes of the survey was identification that our hypothesis as a research question was deemed important and of paramount importance for the UK obstetricians with three quarters of respondents supporting our research question[121]. They also identified “gestation at delivery” as the most important primary outcome for the future randomised controlled trial to test our hypothesis and address the question of what is the best type of suture material to be used for planned cervical cerclage, multifilament braided or monofilament material?

Conclusion

As part of the process of establishing a randomised controlled trial we decided to find out a general consensus from obstetric professional community on the topic of cervical cerclage and suture material used and to investigate whether our hypothesis should be challenged.

This survey revealed a significant variation in current practice with regards to patient selection criteria, indications, technique and the number of procedures performed per year. Use of suture material for cerclage is largely homogenous with 86% using Mersilene, which is not evidence based. The majority of obstetricians were in equipoise with regards to the best suture material to be used for cerclage with 78% of participants considering our research question of great importance.

Chapter 5- Rationale for COTS study

5.1 What is pilot/feasibility study

Pilot feasibility project is a miniature of the main trial. The Concise Oxford Thesaurus gives a definition for the pilot study as a preliminary, exploratory test, trial or try out investigation, experiment[148]. Quite often pilot studies are viewed “vanguard trials” i.e. pre-studies. The pilot study tests the new idea or hypothesis and identifies whether the main trial is possible to run with established recruitment, randomisation, sometimes treatment and follow up. It often identifies the main aspects that needed for the design of the main trial. The main question to answer is: “Is this study be practically achievable?” and if yes, what are the important parameters which need to be taken into consideration? The design of the pilot study will very much resemble the design of the planned main trial. Sometimes the difference could be in time scales or fewer measurement points which are usually shorter, making pilot studies quicker and less expensive. Sometimes pilot studies collect the data which will not be a part of the main trial but does contribute significantly to the main trial design. For example, qualitative interviews with participants. Outcomes of those interviews can influence on recruitment procedures in the main trial.

Pilot and feasibility studies quite often overlap but at the same time they each have their own characteristics. A pilot study, as mentioned before, is a small version of the main full-scale trial. It is done to test feasibility of methods, procedures, techniques, sometimes interviews, survey or a particular research tool. Pilot studies usually test research protocol, its acceptability to patients and involved clinicians. There are several limitations of pilot studies. The most important is problems with the wrong conclusions/assumptions being drawn from the pilot data available. This can arise through problems with data contamination and funding issues [149]. The other main issue is that pilot studies are quite often under reported which leads to potential replication of mistakes. Possibly journals are not in favour

of publishing data which doesn't contain any significant statistical results. Well-designed and properly conducted pilot studies can provide information about the best research process and sometimes gives clues to the likely outcomes of subsequent studies.

A feasibility study is conducted to evaluate individual important components for the main trial. They are used to collect information to establish the feasibility of main study, its design and different processes. Some authors even developed guidance on maximising the effect of the qualitative component in feasibility trials for future RCTs[150]. Nevertheless, irrespective of differences, feasibility studies are often called pilot feasibility studies as the goals are almost the same. Most investigators and researchers would use those terms interchangeably. However, MRC and NIHR give exact distinctions between the two. NIHR, for example, sees pilot studies as a part of a main trial, sometimes a first phase of substantive study.

"a version of the main study that is run in miniature to test whether the components of the main study can all work together. It is focused on the processes of the main study, for example to ensure recruitment, randomisation, treatment, and follow-up assessments all run smoothly. It will therefore resemble the main study in many respects, including an assessment of the primary outcome[151]". Whereas MRC considers both types of studies very similar and following the same goals and aims.

5.2. Why do we need pilot studies?

Some authors[152, 153] suggest that there are four main reasons why pilot studies should be performed: 1) process- to identify feasibility of the steps needed to undertake in the main trial; 2) resources- identify financial difficulties which could be faced in the main trial and

calculate budget for the main-scale trial; 3) management- involves planning of the management of human resources involved in the study, necessity of managing data at involved centres etc; 4) scientific- which assesses the safety of the suggested methods of treatment and response to it, or any other intervention[154].

Because pilot/feasibility studies are the preliminary studies, they have to make sure that they follow certain goals and objectives that can convince the funding panels. First of all, they have to prove to funding bodies that data collection will be performed in the way to answer the question whether the main trial is feasible. Secondly, in both types of studies the main objective should be the estimation of recruitment rates. Even when researches are convinced about high recruitment rate, funders would want to see reassurance from the small scale pilot study.

So, based on the results of three pieces of preliminary work; namely a retrospective dataset analysis, systematic review and a national survey I have justified a rationale for running a pilot/feasibility study to look at the outcome of pregnancies with planned cervical cerclage depending on the type of suture material used during the procedure to funding bodies. The rationale included several important points:

1. PTB is one of the major challenges in Obstetrics and Neonatology globally
2. A UK wide survey of Consultants obstetricians confirmed that there is variation in practice and they are not sure about the best type of suture to be used for the cerclage
3. A significant number of clinicians are in equipoise as to which is the best suture material to use
4. There is an emerging evidence about significant complications with braided non absorbable mesh-like suture material in ophthalmology and urogynaecology

5. Our meta-analysis suggested a significant risk reduction in pregnancy loss when using monofilament sutures

6. It is possible that the actual effectiveness of this surgical procedure is reduced by the potential harm of the type of suture material that is commonly used for this procedure

5.3 Research protocol

I have developed trial documents (**Appendix 3,4,5)** and initiated a pilot/feasibility study. The key trial document was a research protocol, which is presented in this chapter and has been published in Trials Journal[155] in October 2014. Protocol writing usually precedes application for ethical approval and registration. COTS gained Ethical approval from Edgbaston Research Ethics Committee (COTS REC reference 12/WM/0141) (see letter of approval attached in **Appendix 6**) and was registered with the International Standard Research for Clinical Trials(ISRCTN17866773) on 27 March 2013. Full text of the published protocol is online: http://trialsjournal.biomedcentral.com/articles/10.1186/1745-6215-15-415.

Because of self-plagiarism regulations I haven't included the whole protocol into this chapter as the wording of this work could not be modified. The research proposal for COTS was developed in a multidisciplinary manner and in conjunction with other disciplines and I acknowledge the contribution of these. The groups included obstetricians, midwives, statisticians, qualitative researchers, service users, the Birmingham Clinical Trial Unit (BCTU) team (see letter of support **Appendix 7**) and the Research and Development department at Birmingham Women's Hospital. External groups who contributed included the local BBC CLRN (Birmingham and Black Country Comprehensive Local Research Network) support and RCOG national preterm labour CSG (Clinical Support Group). The research

proposal was presented to both of these groups and feedback and comments were addressed and included into the final version.

5.4.1 Format of research protocols

The World Health Organisation (WHO) has a recommended format for developing research proposal/protocols. Firstly, each protocol should start from the title and registration date followed by general information which is the name of investigators who are conducting the research with their titles, responsibilities and contact details as well as the name of sponsor or funder of the study, if any. It is recommended that the title contains a summary of study design, treatment/intervention, comparators or placebo, population and indication, and sometimes the setting[156].

One person should be identified as Chief Investigator or Principal Investigator. It is usually the Senior researcher or MD/PhD student who has overall responsibility for the design and running of the study. If the research is clinically based, then the protocol should include the name and address of the institute, hospital or clinical laboratory where the research was conducted. Each protocol is assigned a version number, draft and date. This is important as then any changes can be tracked by Research and Development departments or Ethics Committee if the protocol needs to be modified in the future. The signature page will include signatures of all professionals involved in the study.

The protocol should have well formulated reasons, based on the knowledge available, for conducting the particular research study. This includes the rationale or summary, followed by the goals/objectives and study design. In the COTS protocol I have described reasons for initiating the study based on information obtained from the literature search, systematic review and national survey and they are presented in the next chapter. I have formulated

the hypothesis and justified the reason for conducting a feasibility study. In the final published version, I have also included strengths and weakness of the study, as per requirements of Trials journal. The main weaknesses of the study were the inabilities to calculate sample size and estimate recruitment and attrition rate. However, the main strength was the understanding and support of our hypothesis by leading clinicians in O&G field in UK, RCOG Preterm birth specialty group and PPI (Patient and Public involvement) group.

Any research protocol should include the flow chart which is a summary of the patient pathway through the study. My flowchart Fig 3. clearly states the population (participants) - women eligible for elective or ultrasound indicated cerclage between 12 to 21+6 weeks of gestation.

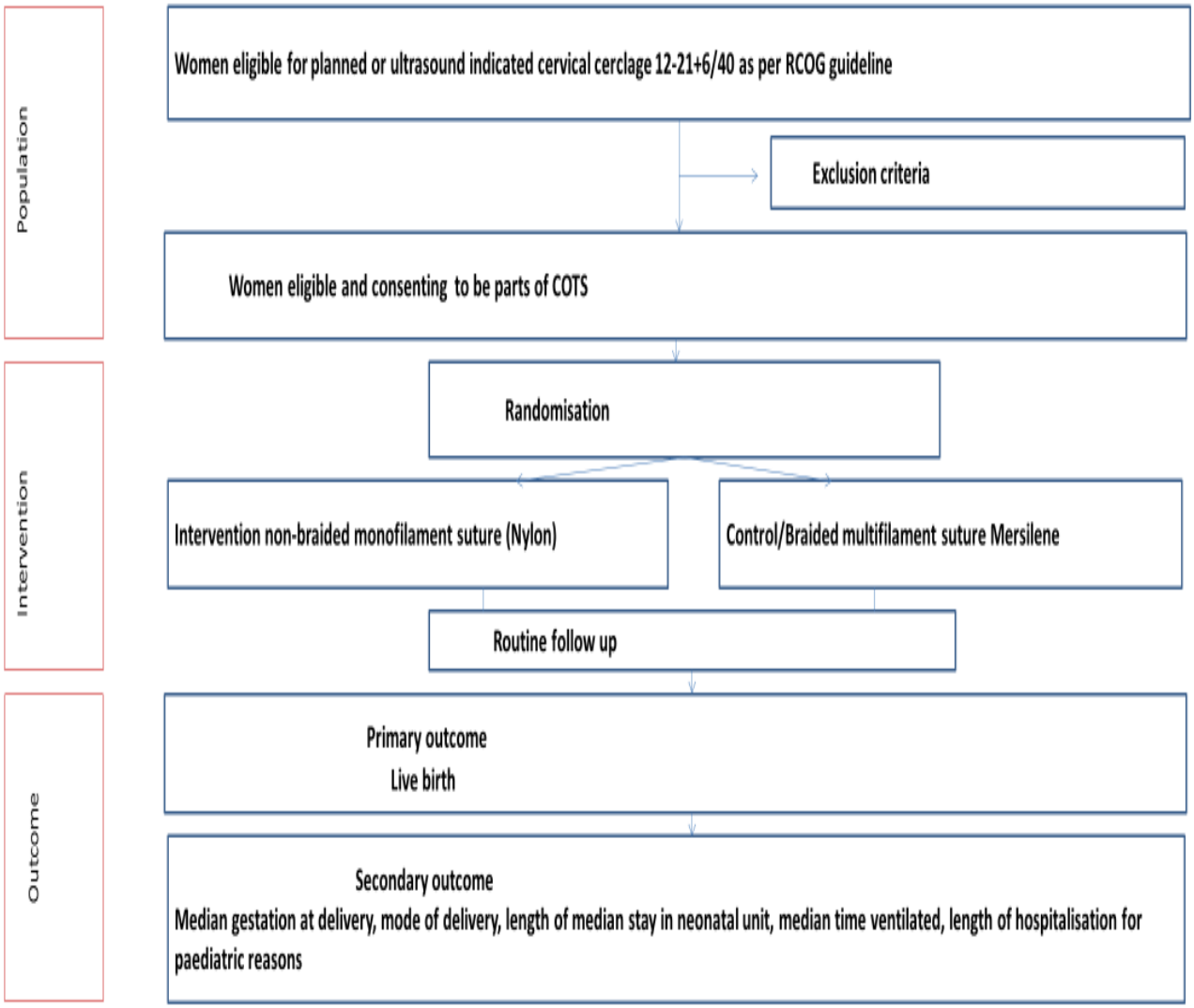


Figure 17. COTS study flow chart

Based on inclusion criteria only eligible participants can be randomised to two groups which according to flow chart is under intervention section. Subject selection is also important:

1) Number of recruitment centres.

2) Source of participants for the study.

3) Inclusion and exclusion criteria.

With regards to recruitment, the process should be described in details including the method of recruitment (clinics, social media, adverts, university or hospital websites etc.), issues around consent (who will gain the consent and where, arrangements for non-English speakers, provision of patient information leaflet), payment to participants if any and, details of any tests required to assess eligibility to be included into the study.

The intervention part of the protocol should give general information about intervention and control. In our case this included information about both types of suture material and detailed description of exactly how treatment (cerclage) is going to be performed and by whom. The intervention part should be followed or preceded by randomisation details. If a study is randomised, then researchers should specify type of randomisation: (e.g. simple, cluster, stratified, block, minimisation) and how many arms with details of whether the allocation is equal or unequal and, if the latter the allocation ratios. In blinded studies the allocation should be concealed (sealed envelopes, computerised etc.). The randomisation schedule should be described in detail including information on how it is going to happen, where, who is going to randomise, which randomisation pads are going to be used and out of hours rules. Researchers rely on the blinding procedures to improve the quality of their data and to avoid bias. In the case of COTS blinding was neither possible nor ethical. In view of logistic difficulties of ensuring blinding of participants and the fact that all the COTS outcomes were objective measures that were easily and independently retrieved from hospital records and hence unlikely that the lack of blinding was a cause of serious bias; we did not intend to attempt blinding participants or their assessors. Additionally, it was theoretically possible that the clinicians involved in the routine clinical care may require immediate access to this information.

The study design and type of trial should be clearly stated and justified. COTS was a pilot/feasibility study as the preparation for the main trial. At the same time, it was a randomised controlled trial which we used to test recruitment, attrition rate and problems which can be faced with randomisation.

The study provided the research team with a unique opportunity to identify and prepare for the challenges and uncertainties of evaluating the clinical interventions within a larger RCT. Conducting this study gave an opportunity to assess the acceptability of the study interventions to women with cervical incompetence; test the study protocol; and facilitate a formal sample-size calculation for the definitive study Cerclage Suture Type for an Insufficient Cervix and its effect on Health Outcomes (C-STICH). Ultimately, it enhanced the scientific rigour and value of the full-scale study.

The methodology part of the protocol is of paramount importance. It should contain information on interventions involved, investigations to be carried out and procedures. Interventions should be described in detail, especially if any medicinal product or device is tested or used. In the case of COTS, I gave a full description of both types of suture material which is Mersilene tape and Nylon or Prolene sutures (depending on its availability in units involved in recruitment for COTS).

In order to obtain the large number of patients necessary for the reliable evaluation of the best suture to use for cerclage, the trial needed the participation of several centres. To make this practicable, trial procedures needed to be simple, with minimal additional workload placed on participating clinicians, beyond that required to treat their patients. This was achieved by simple entry procedures (a single phone/fax call to the randomisation office), routine follow-up of patients (with few additional hospital visits or tests to be performed

above those done as part of standard care), minimising documentation and largely patient-based evaluation of outcome.

The pilot and feasibility randomised controlled trial (RCT) was conducted in three maternity centres in the UK in order to assess likely recruitment rates and acceptability across different sites.

Safety considerations need to be clearly described in protocol explaining how safety of research participants will be protected. The protocol had a list of SAEs (Serious Adverse Events) and clearly specified as Serious adverse events believed to be due to cervical cerclage. This was reported on a Serious Adverse Event form and should have been faxed to the **COTS** study office on the number provided. SAEs still present at the end of the study must have been followed up at least until the final outcome is determined, even if it implies that the follow-up continues after the patient finishes the study treatment and, when appropriate, until the end of the planned period of follow-up. The BCTU was supposed to report all SAEs to the DMEC (Data Monitoring Committee) approximately 3-monthly, to the main REC annually, and to the Trial Steering Committee 6-monthly. Local Investigators were responsible for reporting SAEs to their host institution, according to local regulations, but they did not need to inform the main REC as this was done by the BCTU.

Both suture materials tested in COTS are standard surgical sutures that are currently used for this procedure throughout the UK; hence, we were not anticipating any serious adverse events related to the surgery. However, Serious Adverse Events believed to be due to cervical cerclage were planned to be reported on a Serious Adverse Event (SAE) form.

Project management section involved procedures on trial organisation and described responsibility of each member of team. The organisation of the trial was specified in order

to ensure the smooth running of **COTS** and to minimise the overall procedural workload. It was proposed that each centre should designate individuals who would be chiefly responsible for local coordination of clinical, pathological and administrative aspects. The **COTS** Trial Office, worked together with NCRN networks, and provided as much assistance as they could to local co-ordinators and investigators in obtaining Trust approval in each centre. The protocol should describe any potential ethical issues which can arise during study and cause ethical concern. I have clearly stated that conduct of the trial at each recruiting site including confidentiality and storage of all personal and research data would be in accordance with all applicable research governance regulatory requirements. All recruiting maternity units were required to sign a clinical trial agreement document detailing their commitment towards complying with the relevant laws, regulations, codes of practice and obligations to publication. Site specific and Research and Development approval was required for each recruiting unit.

A Trial Steering Committee (TSC) was convened to provide overall supervision of the COTS study and adhered to the Medical Research Council (MRC) Guidelines for Good Clinical Practice. Any deviations from the clinical trial agreement were monitored by the TSC who would decide whether further action needs to be considered. An independent data monitoring ethics committee (DMEC) was convened for the COTS study by the sponsor and acted as an advisory committee to the TSC.

The protocol should provide information on how data will be managed[156]. All personal information in COTS trial, received in paper format for the trial, was held securely and treated as strictly confidential according to BCTU policies. All staff involved in the COTS Trial (clinical, academic, BCTU) shared the same duty of care to prevent unauthorised disclosure of personal information. No data that could be used to identify an individual was so far

published. The data was entered on a secure computer database, either directly via the internet using secure socket layer encryption technology or indirectly from paper by the COTS Clinical Research Fellow (myself). Data was stored on a secure server at BCTU under the provisions of the Data Protection Act and/or applicable laws and regulations.

The budget or financial section of the protocol should specify about the funding received. **COTS** was funded by Birmingham Women's Hospital Urogynaecology Research Fund and organised by the University of Birmingham Clinical Trials Unit. The **COTS** trial didn't offer any financial support to the collaborating hospitals for treatments. However, **COTS** did not involve any extra research costs for participating hospitals. The current standard of care is insertion of the cervical suture electively between 12 and 16 weeks of pregnancy. No additional follow-up visits or investigations were needed other than those that would normally be required for standard patient care. With regards to compatibility with other studies, COTS was the only study that was planning to explore different sutures used for cervical cerclage and associated outcomes. **COTS** was not an industry-sponsored trial, ABPI (Association of the British Pharmaceutical Industry) guidelines on indemnity did not apply and there were no special arrangements for compensation for any non-negligent harm suffered by patients as a result of participating in the study. The normal NHS indemnity liability arrangements for clinician initiated research applied (NHS Executive Health Service Guidelines HSG (96) 48, 8th November 1996). It was noted, however, that negligent liability related to the standard of care remained the responsibility of the hospital, whether or not a patient is part of a clinical trial, because of the duty of care that the hospital has for its patients.

The research protocol had information on the duration of the trial with a detailed month to month activity; expected outcomes; and results dissemination policy. CVs of all investigators were attached.

Chapter 6- COTS study and results

6.1 Objectives for COTS study

Main objectives of the COTS study:

- Testing trial documents, especially assessing whether the research protocol is realistic
- Identifying the number of eligible patients and ways to identify and approach them in order to maximise the recruitment
- Gauge the acceptability of the research plan with the women participating in the study and the clinicians involved
- Engage women in all aspects of the study and determine what outcomes are important from their perspective
- Identifying willingness of participants to be randomised
- Estimate likely attrition rates
- Assessing the willingness of clinicians to recruit participants
- Predicting the time needed to collect the data, problems with data clearing and analysis
- Finalising the costing, including time involved, education and training, administration and organisational issues
- Evaluating the service delivery and financial implications on the organisations involved in the research study
- Providing the basic justification for applying for different grants and trying to convince funding bodies and other stakeholders that research team is sustainable and main study is feasible

- Establishing the likely success of the one type of suture over the other in cases of elective cervical cerclage.

Feasibility studies are not usually designed to evaluate the outcome of interest and this was true in our case where we had already decided on the primary outcome. That is usually left to the main trial. The most important thing though that the sample for a pilot project should be representative of the target population of the main trial, obviously inclusion/exclusion criteria should be the same in the pilot and the main trial. Feasibility studies are used to inform on power calculations and sample sizes hence COTS didn't have formal sample size calculation. The size of the pilot study will not allow reliable assessment of the effect of the intervention on clinical outcomes. In the pilot study, analyses will principally take the form of simple descriptive statistics of process outcomes, including eligibility and recruitment rates, and of live birth rate and secondary clinical outcomes, to aid designing of the main trial. Regression models, appropriate to the forms of data, will also be fitted, to allow adjustment for covariates. The systems and data collection tools will be developed and piloted. These include the telephone randomisation system and the collection of the clinical data from both woman and baby prior to discharge from hospital.

6.2 Preparatory work for the main trial

COTS was undertaken into preparation for C-STICH. While running the pilot feasibility trial I have applied for several grants in order to secure funds for implementation of the main trial. The sequence of applications is following: Springboard Fellowship, Spark Clinical Research Fellowship scheme, Evelyn Trust, Wellbeing of Women research grant, Action Medical Research (AMR) and finally Research for Patient Benefit (RfPB) followed by Health

Technology Assessment (HTA). Each subsequent application provided us with valuable feedback and information which re-shaped the final definitive study. There were two main recommendations out of all applications, which had significant impact on strengthening the study. First one from AMR where the reviewers highlighted the clinical relevance, clarity and importance of the proposed research question, its potential impact on health services and social care and the clinical and academic rigour of the research team. However, it was suggested that the application would be strengthened by:

1. A more thorough justification of study design: As a result, I have sought advice and input from the Birmingham Clinical Trials Unit (BCTU) and the West Midlands Research Design Service (RDS) regarding the study design. Following this consultation, it was deemed more suitable that we redesign COTS as a pilot/feasibility study to test procedures for recruitment & randomisation, estimate recruitment and attrition rates, test data collection procedures and confirm the level of resource required to ensure the successful delivery of a full study.

2. Demonstrate the relevance of outcome measures amongst peers: With the help of BCTU and RCOG I have conducted a national survey of UK consultants who prioritised the importance of different clinical outcomes. Significantly, the primary outcome selected for COTS rated highest in the survey, hence supporting its clinical relevance.

3.Reviewing current evidence: I have undertaken systematic review of randomised and non-randomised studies to prove that the research question could not be answered by available primary research.

The next major milestone in the history of the COTS application was feedback from RfPB (ref PB-PG-0212-27119) (**Appendix 8, Appendix 9**). The RfPB review panel highlighted the importance of the proposed research question. However, the panel suggested that our team

should aim for a full-scale study and recommended that we apply for NIHR Health Technology Assessment programme.

The reviewers agreed that there was a clinical, scientific and ethical need for this full scale RCT to investigate the basic question of the influence of type of suture material on the outcome of cervical cerclage. They commended the appropriateness of the proposed research design for evaluating an intervention. They confirmed that work plan and project management plans were realistic and adequate. They recognised the expertise of the research team in, that, it included all appropriate clinical and methodological specialists and that members were very well coordinated. However, some reviewers raised a concern about the potential difficulty in engaging with other clinicians who might not wish to change their practice, which can potentially affect recruitment into the study. They thought that this may be problematic and could potentially pose difficulty in reaching recruitment targets. In view of this issue and because of moving to planning a full scale trial we have approached several clinicians who are national experts in the field of preterm labour and high risk obstetrics who has agreed to participate in the main trial. RfPB advised:

1. To be more robust in terms of patient's numbers as well changing study design
2. Warned about problems with recruitment, as women may not wish to have "suture which is possibly associated with higher risk of infection" and the biased nature of the medical team also may make recruitment difficult.
3. Advised on standardisation of surgical procedure for inserting the suture.
4. PPI involvement should expand and PIL needs to have more lay language

All that was taken into consideration especially PPI involvement and editing PIL. We have presented COTS to the Parents and Researchers Involvement in Maternity (PRIME) group (**Appendix 10),** a PPI group set up in collaboration with the University of Birmingham

CLAHRC (Collaboration for Leadership in Applied Health Research and Care) and has a geographical and socio-economically diverse spectrum of women with experience of Maternity Services use and their partners. The group supported COTS and agreed to provide the required lay representation on the study steering committee and promised to help with main trial. To alleviate anxiety of study participants after surgery, they suggested that when approaching women to participate, the possible risks associated with each suture material should be explained in general without specifying which material is associated with which risk.

In preparation for HTA grant I attended numerous conferences and research meetings (**Appendix 11)** in order to familiarise obstetric and fetal medicine community with the objectives of COTS and get their support and recommendations. For example, COTS was presented at Birmingham and the Black Country Comprehensive Local Research Network BBC CLRN, Maternal Medicine and Preterm Birth CSG held at BMFMS, got endorsement from REACH (Reproductive and Child Health) group and RCOG pre-term CSG (Clinical Studies Group). I have also attended Surgery Research Writing Workshop organised by National Institute for health Research in London, in preparation for HTA application. Poster was presented at joint Annual Academic Meeting (RCOG) and Blair Bell Research Competition.

6.3 Recruitment

6.3.1 Ethical approval

Initially a favourable ethical opinion was granted by NRES Committee West Midlands - Edgbaston to the study with title: A pilot/feasibility RCT comparing monofilament(intervention) versus multifilament (control) suture material for elective cervical

cerclage in the management of suspected cervical incompetence, with reference number 12/WM/0141 (**Appendix 6**) based on information described in application form, protocol and supporting documentation.

6.3.2 Trial documents and PPI group

The application form was filled through IRAS (Integrated Research Application System). It is an online system for applying for permissions and approvals for health and social care/community research in the UK. Supporting documentation, was developed before the application process commenced, included consent form, patient information sheet, letter to GP. The patient information leaflet was developed in conjunction with PPI (patient and public involvement) group. Their suggestions had a colossal impact on the way information was presented in the leaflet and as a result improved process of recruitment. The language and the content of the PIL became more accessible and appropriate. The women involved in PPI group had personal experience of midtrimester loss.

PPI involvement (engagement, participation) in research projects are of paramount importance, especially in advice regarding study design, defining outcomes for the studies and developing research documentation, for example PIL etc. Members of public and patients may have personal experience of particular research topic and can provide researchers with their own perspective. Their knowledge and experience are usually quite different to researchers even though latter are experts in the field. A recent review by Staley (2009)[157] found that public involvement was reported to be of particular value in clinical trials where it helped to improve trial design and ensured the use of relevant outcome measures.

In 2009, Professor Dame Sally Davies wrote[157]: " No matter how complicated the research, or how brilliant is the researcher, patients and public always offer unique, invaluable insights.

Their advice when designing, implementing and evaluating research invariably makes studies more effective, more credible and often more cost efficient as well." It is quite important to understand why do you want to involve public members in your research and identify who are those people. I have worked closely with a group of consumers and that has intrinsically changed all the researchers' attitudes to the project and involvement itself. I wanted to involve women with previous experience of preterm birth and SMTL or those who had a cerclage procedure as a treatment for those conditions with positive or negative outcome. It is preferable to involve more than one person. The advantages include that you can involve them at different stages, give them a choice what they would want to be involved in, they can provide support for each other if needed, so that a range of opinions can be expressed and to be guaranteed involvement if one is ill or withdraws from the participation. As COTS was the pilot project, it was particularly important to actively involve users in design and management of the study. Two women with previous experience of SMTL and consequently cervical cerclage were recruited and agreed to be involved in the reviewing and provide feedback on trial documents including patient information leaflet and trial questionnaire. It made information clearer and more accessible as they made language and content of PIL more accessible for public. The primary outcome for the study was also selected in conjunction with patient group represented by patients with history of pregnancy losses in the past.

A member of public was also able to advise on the Lay Summary (**Appendix 12**) for RfPB and HTA applications for the main trial. She was invited to sit on the Trial Steering Committee during the project lifetime and work in collaboration with research team from reviewing protocol documents to dissemination of the results, as evidence suggests that public involvement has had greatest impact when people have been involved through the

entire research project, rather than just at discrete stages. Her participation in the project was within the frames of INVOLVE (2009) report recommendations[157] on best practice for patient and public involvement. According to INVOLVE it is better to involve people at early stages of the study so they would have ownership of the research and feel part of it.

6.3.3 Sands involvement

Sands (Stillbirth and Neonatal death charity) was actively involved in COTS project. This organisation has national credibility and network to reach the broad geographical base of women and their partners affected by death of baby before, during or after birth. They provide support (emotional and informational help) to people through on-line forum, email, support groups or phone line. They have 3 core aims:

- To support anyone affected by the death of a baby
- To work in partnership with health professionals to improve the quality of care and services offered to bereaved families; and
- To promote research and changes in practice that could help to reduce the loss of babies' lives

The research and prevention manager of Sands gave valuable advice on Patient and Public Involvement. She was in charge of any future PPI involvement for the main trial through their organisation.

After gaining Ethical approval for the project all necessary paperwork was forwarded to Research and Development departments of the three hospitals where the COTS study was implemented: main site- Birmingham Women's Hospital NHS Foundation Trust, Birmingham City Hospital and Cambridge University Hospitals NHS Foundation Trust (Addenbrookes Hospital) (see letters of access attached **Appendix 13**).

6.3.4 Recruitment process

The recruitment process involved screening of hospital notes in antenatal clinics on regular basis and identification of the patients who can be potentially eligible for elective cerclage procedure. In order not to miss any patients, theatre personnel were contacted and left with special note in booking office asking to contact the Research Fellow(myself) in case a cerclage procedure is booked. In this case contact details of the patient were collected and patient was telephoned or emailed (approved by Ethics Committee).

If patients were identified in antenatal clinic, then after consultation with medical team I had a conversation with them about the study and provided them with participant's information leaflet. The dates for cerclage procedures were always available in advance from theatre registry. Patients were contacted in the morning of the day of the procedure. Patients would then sign 3 copies of the consent form if they were happy to participate in the study. Multiple copies were in line with GCP so that a copy is given to the women, one is kept in the patient notes and the third in the local site file. Again in accordance with GCP the GP was notified about their participation in the study. All women approached were recorded on the screening log, available in the investigator site file.

The recruitment process was started at Birmingham Women's Hospital and then initiated at Addenbrookes Hospital and Birmingham City Hospital. Most of the patients were recruited at BWH (11/19), rest at Birmingham City Hospital and none at Addenbrookes. Problems with recruitment at other sites (different to BWH) were mainly due to the absence of a research fellow in the unit. As this was an unfunded pilot, recruitment was dependent on the availability of a research registrar, myself, for approaching, consenting and randomising women presenting to a number of obstetricians at each site. There were a few issues at

each site. For example, at BWH there wasn't a preterm clinic so as a result patients were spread among various antenatal clinics. There were quite a significant number of laparoscopic cerclage procedures performed at BWH which had an impact on recruitment as well, however 100% consented at BWH all had procedure according to allocation. At City Hospital Birmingham there was a problem with availability of the interpreters to translate for recruitment process so as a result few patients were recruited but none was happy to be randomised.

6.3.5 Randomisation

Randomisation is the method used in clinical trials and other experiments in order to reduce bias. In clinical trials randomisations should allow every patient to have a balanced chance of receiving treatment or intervention (depending on the trial design treatment allocation). Randomisation is an important tool which allows to test efficacy of intervention or treatment. Randomisation requires generation of randomisation schedules. Through those schedules random numbers are obtained and given to each subject/intervention/treatment condition. Those random numbers can be generated by the computers or be taken from random number tables[158].

Birmingham Clinical Trials Unit provided randomisation services for the COTS trial. The BCTU is a partner in the Birmingham Surgical Trials Consortium, one of 5 centres designated by the Royal College of Surgeons as specialist surgical CTUs, and has conducted several trials in fetal medicine/ gynaecological surgery (including NIHR HTA trials PLUTO (07/01/44), OPT (06/404/84) and FEMME (08/53/22)).

The patients were randomised immediately just prior to the cervical cerclage procedure in order to minimise the number of withdrawals and protocol violations, but with enough time to ensure the obstetricians were able to prepare the sutures for the procedure. Patients were randomised to one of the arms: Monofilament suture Nylon or Prolene or Multifilament/braided Mersilene tape. I used telephone randomisation with a computer minimisation algorithm, with 1:1 allocation ratio. To reduce the potential for bias telephone randomization occurred immediately before surgery. Randomisation Forms were provided to investigators and used to collate the necessary information prior to randomisation. All questions on the Randomisation Form were answered before a trial number and allocation was given. Once all eligibility criteria were provided a trial number and treatment allocation was given. This process was followed by a confirmatory email sent to the randomising investigator and local Principal Investigator. In this case it was me as randomisation only happened at Birmingham Women's Hospital. No randomisation took place at Birmingham City Hospital as none of the approached participants were happy to be randomised.

It was impossible to blind the obstetrician performing the procedure to the type of suture material used. In view of the fact that all the COTS outcomes are objective measures which would be easily and independently retrieved from hospital records it was deemed unlikely that the lack of blinding would be a cause of significant bias.

Both sutures used in COTS were standard surgical materials already in use in NHS hospitals so no additional cost was involved, and CE marked for this purpose. Mersilene® is a non-absorbable, braided, sterile surgical suture composed of poly-ethylene terephthalate. Ethilon is a non-absorbable, monofilament, sterile surgical suture composed of the long-chain aliphatic polymers Nylon 6 and Nylon 6,6. Both sutures are marketed in the UK by Ethicon. For this pilot study cerclage insertion procedure wasn't standardised. The technique

of suture insertion was at surgeon's discretion. Removal of the suture didn't require any specific guidance. So Consultants involved performed cerclage using McDonald or Shirodkar technique. All other aspects of postoperative management of patients for example tocolysis, progesterone, etc was again at discretion of the consultant in charge of care. At the time, there was no guideline on the management of women with cerclage in situ, so care was individualised depending on care-providing clinician.

6.4 Data collection

The data on all patients enrolled into the study was collected through the main hospital notes and separated into randomised and non-randomised groups, using data collection proforma (**Appendix14).** Those patients who were not randomised were still happy for the outcome of their pregnancy data to be collected.

Number of women approached BWH=16 BCH=9	Number of women eligible BWH=16 BCH=9 Number of women declined BWH=8 BCH=9	Number of women randomised BWH=**8** BCH=0

6.5 Outcomes

As COTS was pilot/feasibility study data was not analysed and this only had a descriptive character. There was no difference noted in outcome of pregnancies depending on type of suture material used.

I was planning to run the pilot/feasibility study in 3 centres with significant numbers of cerclage procedures performed. The objectives, as mentioned before, were few and they had to determine recruitment and retention rates, to assess women's propensity to consent to participation, and to define presentations where randomisation was unfeasible, in order

to identify barriers to recruitment in the main trial. The aim was to target all potentially eligible women undergoing cervical cerclage, capturing reasons for ineligibility, refusal, and preferences for or against particular suture material or number of instances where the trial was never proposed to the patient.

The major issue for all centres was absence of staff directly involved in recruitment and randomisation. As COTS was an unfunded pilot, recruitment was dependent on the availability of a research registrar (myself) for approaching, consenting and randomising women presenting to a number of obstetricians at each site. The research fellow (myself) was based at Birmingham Women's Hospital and as a result all patients who were finally randomised were recruited there. All had procedure according to allocation. Randomisation minimisation was used in order to minimize imbalance between treatments taking stratification factors into account.

Nevertheless, it was still difficult to identify potential participants, as at the time of the pilot there was no preterm birth clinic at Birmingham Women's Hospital and patients were referred to various antenatal clinics. When I moved to Birmingham City Hospital, recruitment at Birmingham Women's Hospital continued with the support of a research Nurse who worked for the department of urogynaecology, covering a few research projects. She was able to recruit 1 patient into the study.

A unique issue for BWH was a significant number of laparoscopic cerclages were offered, accepted and performed for the suspected cervical incompetence. This also decreased the number of potential patients to be approached for COTS pilot.

Recruitment at Birmingham City Hospital faced some major problems as well. The most important one was language barriers when communicating with potential participants. As

COTS was an unfunded study, we had no resources allocated for interpreting services. Thus where possible friends and relatives or members of staff were involved in translation. As a result, we faced significant misunderstanding regarding aims of the study, reasons to participate and benefits of participation for the patients themselves. A second issue was unwillingness of the Consultants involved in provision of cerclage service at Birmingham City Hospital to help with recruitment. They were directly involved in preterm birth prevention clinic service provision but on regular occasions, when I wasn't present there due to rota commitments, missed the opportunity to provide information about participation in COTS study to potentially eligible patients. Also, most of them were not willing to place a suture as per randomisation allocation, in case one would take place, and warned me about it in advance, as they had their own preferences, not supported by any evidence but from experience with a preference for Mersilene tape over Monofilament sutures. As a result, I was unable to recruit successfully at BCH but this "failure" highlighted lots of important issues related to recruitment, which should be avoided or prevented in the main trial. That was one of the main objectives of feasibility study. So overall 23 patients were recruited into COTS and only 8 of them were randomised.

Table 9. Number of randomised patients

Total	Randomised	Non-randomised but happy for data to be collected
23	8	14

As COTS was a pilot/feasibility study there was no formal sample size calculation but information from the preparatory work has enabled sample size calculation for the main trial. Based on our NRS meta-analysis, the pregnancy loss rate was 4% and 15% in the non-braided versus the braided suture. In view of the small sample size and lack of randomisation it is highly likely that this effect size was exaggerated. Based on a retrospective data analysis of 49 cases of cerclage using non-braided sutures undertaken in 2 large maternity units, the pregnancy loss rate in this cohort was 5%. In contrast, in the cerclage group of RCTs included in the Cochrane review where braided sutures were routinely used, the cumulative pregnancy loss rate was 13%. Therefore, to demonstrate a more reserved reduction in this risk from 13 to 5% with the use of monofilament sutures we would require 147 women in each group (a total of 294 women) with 90% power (p=0.05). To allow for a 10% loss to follow-up rate we increased the total sample size to 330. Assuming a decline rate of 25%, we would need to approach 400 eligible women to achieve the required sample size.

Randomised								
No	Ethnicity	Parity	Previous PTB/miscarriage	Gestation at insertion	Gestation at removal	Swabs	Type of suture	Mode of delivery
1	Asian (Indian)	2	SMTL at 20/40, followed by 2 NVD with cerclage in pregnancy	13/40	34+3/40 C/S	Candida	Monofilament	C/S
2	Asian(Pakistani)	0	SMTL x 2 at 16/40 and 18/40 Planned cerclage	11+3/40	38+1/40 C/S	Not done	Multifilament	C/S
3	Black(African)	0	SMTL at 22/40 Planned cerclage	13+4/40	36+6/40	Not done	Multifilament	NVD
4	Asian(Pakistani)	2	SMTL at 20/40, followed by2 NVD, both pregnancies had elective cerclage	13+5/40	39+6/40	Candida	Multifilament	NVD
5	White(English)	0	PTB at 26/40, neonatal death, TVS, short cervix on scan offered cerclage	15/40	33+2/40	BV treated	Monofilament	NVD
6	Black British	1	SMTL at 19/40, followed by NVD with planned cerclage at 13/40	15+6/40	37+3/40	No growth	Multifilament	NVD
7	Black (Carribean	0	PTB at 28/40, TVS short cervix	15+2/40	NVD 31+1/40	Not done	Monofilament	NVD
8	White(English)	0	SMTL at 16/40, TVS short cervix	15+1/40	38+1/40	Staph	Monofilament	

Table 10 COTS: outcome data of randomised cohort

Mean parity was 0.6 (range from 0-2). Mean maternal age at insertion was 31. Mean gestational age at insertion was 14.1 weeks (range from 11+3/40 -15+6/40) which is usually the common gestational age for planned cerclage insertion. Mean gestational age at removal was 36.1 weeks (range from 31+1/40 to 38+1/40). The majority of patients had previous SMTL and only two PTB in the past. Those with SMTL had planned cerclage and only one opted for cervical scanning and had ultrasound indicated cerclage. Three patients had a history of successful cerclage insertion in the previous pregnancies and as a result

opted for suture insertion in current pregnancy. The majority of patients in randomised cohort had normal vaginal delivery, two had Caesarean Section performed at 34+3/40 and 38+1/40 both for fetal distress in labour. Unfortunately, swabs were not taken routinely before or after procedure and those taken randomly through the pregnancy presented in the table.

So with regards to pregnancy outcomes depending on the type of suture material, monofilament suture was associated with more cases of preterm delivery before 34 weeks of gestation. But as sample was small though not considered statistically significant.

Neonatal outcome: 2 babies were admitted to NNU for short term and required respiratory support. All babies were discharged home in good condition. Long term follow-up wasn't done as it wasn't the objective of the study.

The study was officially closed on 3rd of April 2014 when all data cleaning and analysis was performed (see letter of closure **Appendix 15**).

Chapter 7- Conclusion

This MD thesis reflects a substantial body of work. COTS was a pilot/feasibility study which provided necessary information to plan and confidently run the definitive trial into the role of cervical cerclage. This work provided the evidence that underpinned C-STICH. It is hoped that C-STICH will determine the clinical and cost effectiveness of the different types of suture material used for elective cervical cerclage and answer the question as to the major flaw in the MRC suture trial of the late 1980's. The scientific question of use of different type of suture material for elective cerclage was never raised by obstetrical community before. This thesis provides the science behind the problems with braided/multifilament sutures in different surgical disciplines which allowed us to hypothesise that their use can have a detrimental impact on outcome of pregnancy. Braided sutures, instead of prolonging pregnancy, could cause infection, which may precipitate premature delivery or miscarriage.

I have described the systematic approach of the COTS programme with its stepwise process, which initially involved retrospective data analysis and later was supported by the evidence from national survey and systematic review. Evidence from retrospective analysis and systematic review confirmed that the research question about the suitability of multifilament/braided sutures in cervical cerclage; and that they may be associated with poor obstetric outcome. The Systematic review confirmed that at the time of writing there were no RCTs addressing this issue. Our national survey proved that this scientific question is of significant interest to the Obstetrical community and that the practice with cerclage varies across the country.

The COTS pilot/feasibility study met its main objectives:

1. We tested all trial documents. As a result, the research protocol was modified as primary outcome for the main trial was strengthened from the live birth rate to

pregnancy loss as was advised by PPI group. The Patient information leaflet was also modified, taking into consideration recommendations from PPI and Sands. It was re-written in more lay language, avoiding term incompetence with regards to cervical weakness. Overall the research protocol seemed to be realistic and the consent form and letter to GP didn't require any changes.

2. We identified that a dedicated preterm birth clinic is the best setting to identify eligible patients and approach them. In units where preterm clinics do not exist the targeting of general antenatal clinics is complex and may be complicated. The process of recruitment and some of the eligible women can be potentially missed. This study helped in the establishment of a dedicated preterm birth clinic at Birmingham Women's Hospital.
3. We have created a PPI group as a part of COTS trial programme. Two women with previous experience of cervical suture placement were involved at the initial design stage. This process ensured that the women's views were heard and the most important outcome to women was eventually chosen as the primary outcome. This has strengthened our belief that PPI involvement is of paramount importance for not just the main trial in this programme, but in all clinical research.
4. The attrition rate was 0%, as after randomisation and suture insertion patients didn't have any additional clinical intervention and any data about pregnancy and its outcome was collected routinely. There were no withdrawals from the study.
5. We raised a concern about the potential difficulty in engaging clinicians who might not be open to the research question and not consider changing their practice, and thus possibly affect recruitment into the study. We addressed this by approaching several clinicians who are national experts in the field of preterm labour and high risk

obstetrics. We have had agreement from lead consultants and clinical academics in 17 units in the UK (cumulative >85,000 deliveries per annum) who agreed to participate in COTS once funding was secured for the main study (C-STICH).

6. The PPI group were instrumental in advising on the willingness of participants to be randomised. They identified possible risk factors associated with each suture type should be explained in general terms without paying specific attention to which material is associated with each particular risk.
7. As a result, we were able to furnish the basic justification for applying to different funding bodies and were successful in securing funds for the main trial.

COTS has proved to be a successful pilot/feasibility study as it has not only met all objectives but also secured funds for the main trial (successful £1.2 million NHR HTA grant) which at the time of writing has recruited 899 women. COTS was successful for several reasons. From the start the study was endorsed by RCOG preterm labour Clinical Study Group. Also we have received the support from REACH (Reproductive Health and Childbirth) the local specialty group CLRN network for recruitment into the study. The research protocol for this study was developed in conjunction with obstetricians, midwives, statisticians, a qualitative researcher, service users, the Birmingham Clinical Trial Unit (BCTU) team and the Research and Development department at Birmingham Women's Hospital. Their experience and expertise made COTS achieve its main goal and secure the grant.

On a personal note I have faced many challenges during the journey of this thesis. COTS was funded by soft monies which had a significant implication on study flow. At the time of the pilot there was no preterm birth clinic at Birmingham Women’s Hospital and patients were referred to various antenatal clinics, there were few laparoscopic cerclage procedures being performed, as one consultant had an interest in this. Recruitment was initially wholly

dependent on the availability of a research registrar as this was not a portfolio study, interpreters were not available to translate and many others which are described in chapter 6. Despite these obstacles COTS was completed and lead to main trial.

If I were to have the time again COTS again I would have done things in the same order. COTS was a learning curve for me. I acquired research skills, understood fully process of gaining ethical approval, developing study documents, applying for different funding bodies, producing scientific papers and participating in research meetings and discussions where your idea is challenged and questioned. I also gained lots of friends and collaborators which the most valuable asset. I have developed both as a clinician and researcher during my time undertaking this work.

Appendix 1- data collection proforma for retrospective analysis

Part A. Demographic data

Hospital number _____ Initials _____

Ethnicity

White
British ☐
Irish ☐
White other ☐

Black/Black British
Caribbean ☐
African ☐
Black other ☐

Asian/Asian British
Indian ☐
Pakistani ☐
Bangladeshi ☐
Asian other ☐

Mixed
Mixed White/Black Caribbean ☐
Mixed White/Black African ☐
Mixed White/Asian ☐
Mixed Other ☐

Chinese or Other Ethnic Group

Chinese ☐

Any other ☐ Not given ☐

Part B. Clinical data

Past obstetrical history _____

_____

_____

Gestation at insertion _____/40

Gestation at removal _____/40

Suture type: Mersilene ☐ Nylon/Prolene ☐

Technique: McDonald ☐ Shirodkar ☐

Surgeon Consultant ☐
SST ☐
SpR ☐

Outcome: NVD ☐ C/S ☐ Other ☐

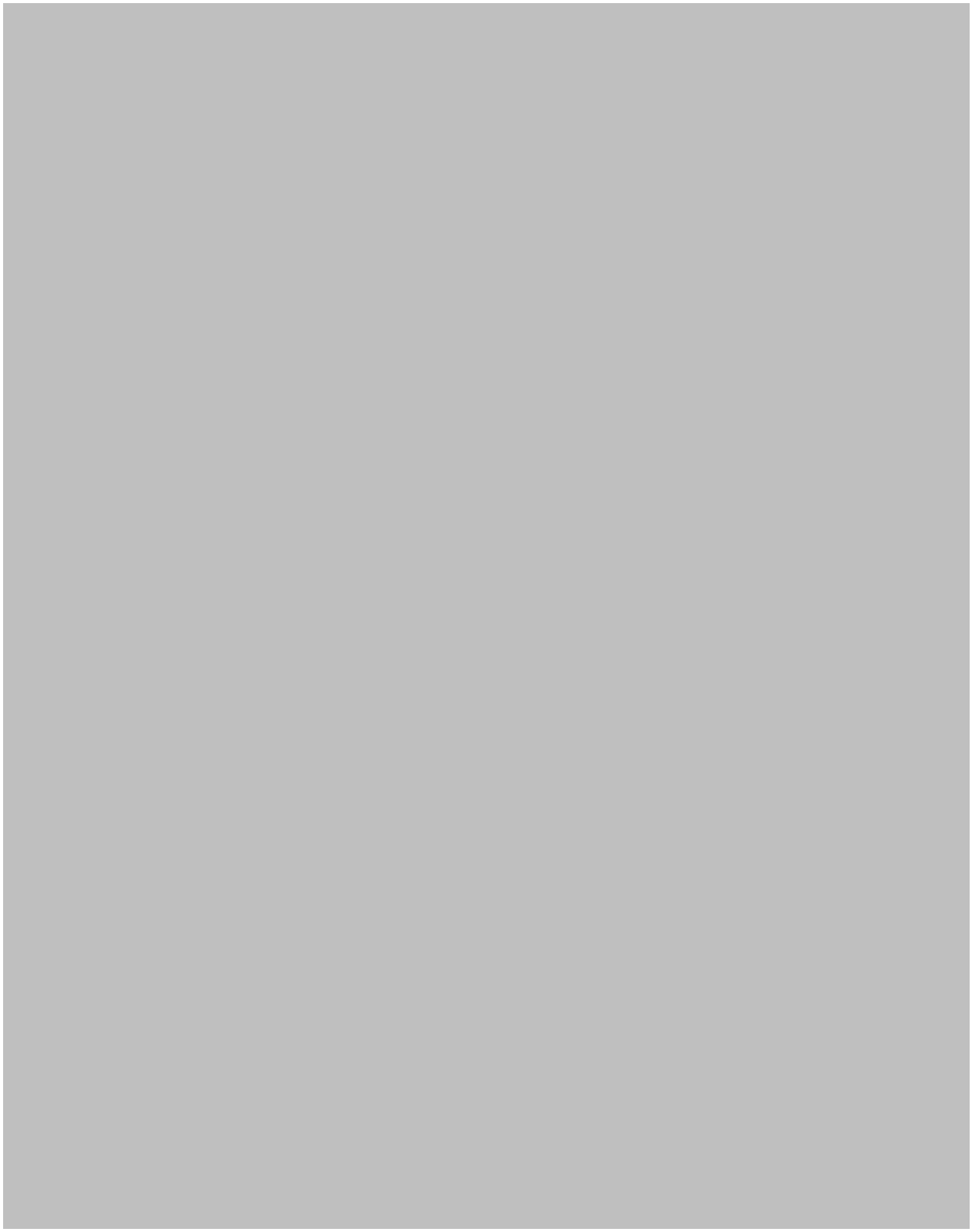
Gestation at delivery _____/40

Swabs taken

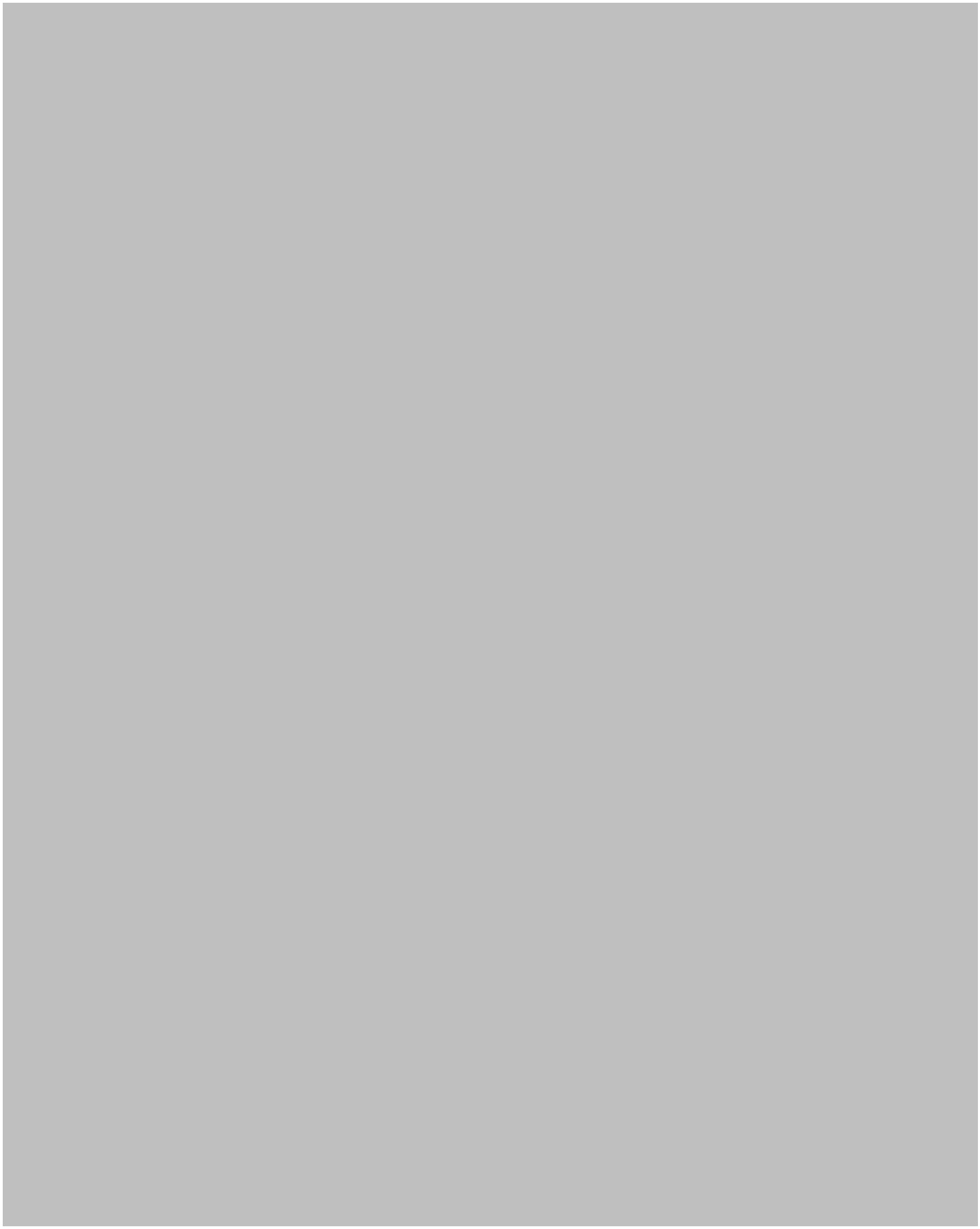
Yes ☐ Growth _____

No ☐

Appendix 2 – Request form for RCOG, page 1



Appendix 2- Request form for RCOG, page 2



Appendix 3- Trial documents, notification letter to GP

Birmingham Women's NHS
NHS Foundation Trust

Doctor
Practice
Street
City
Postcode

Date

Dear Dr <*gp name*>

Name.....D.o.B.....NHS No.....

Your patient, named above, has been recommended an elective cervical cerclage as a part of her pregnancy care and as such suitable for entry to COTS, a pilot/feasibility study looking at pregnancy outcome after elective cervical cerclage in relation to type of suture material used, comparing monofilament (intervention) versus multifilament (control) suture material.

Birmingham Women's Hospital is acting as trial sponsor. The University of Birmingham Clinical Trials Unit are acting as coordinating centre. The study is funded principally by the Birmingham Women's Hospital.

Your patient has been informed about the **COTS** trial, has consented to take part and has been randomly allocated to either Multifilament or Monofilament group.

If you have any queries about the patient's management, please feel free to contact me. If you require any further information about the **COTS** trial, it can be obtained from the **COTS** trial office (see address below). Please file this letter in the patient's notes. I would appreciate being notified if they are no longer one of your patients.

Yours sincerely

Name

Position

Appendix 4- Trial documents, Consent form

Version 1.0 Date 23/04/2012

Birmingham Women's NHS
NHS Foundation Trust

Consent Form

Title of Project: COTS study (Cerclage **O**utcome by **T**ype of **S**uture)

Name of the Researcher: Dr Fidan Israfilbayli *Please initial*

1. I confirm I have read and understood the information leaflet dated 07/06/2012 Version 2 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactory. ☐
2. I understand that my participation is voluntary and I am free to withdraw at any time without giving any reason. ☐
3. I agree to be randomised and be contacted in the future for an interview about trial recruitment ☐
4. I give permission to inform my GP about my participation in study. ☐

   Please choose from the following options remaining:

   a) I agree to be randomised but don't want to be contacted in the future for an interview about trial recruitment ☐

   b) I don't want to be randomised but agree for researches to retrieve information from my medical notes ☐
5. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from Birmingham Women's Hospital NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

_____	_____	_____
Name of patient	Date	Signature
Name of person taking consent	Date	Signature

Appendix 5- Trial documents, Patient information leaflet, page 1

Birmingham Women's NHS
NHS Foundation Trust

PARTICIPANT INFORMATION SHEET

COTS study (Cerclage Outcome by **T**ype of **S**uture)

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish.

Why have I been invited?

You have been approached because your Obstetrician has recommended a cervical stitch as a part of your pregnancy care and as such suitable for this study. Cervical stitches are usually offered to women who have had pregnancy problems in the past usually preterm delivery or late miscarriage which may suggest a weak cervix. A Cervical stitch may reduce this risk by helping to keep cervix closed for longer allowing a baby more time to develop and reduce the risks associated with premature delivery.

What is the purpose of the study?
Cervical cerclage has been used for cervical incompetence for over 50 years. Currently there are two types of stitches commonly used for maintaining the cervix closed. Mersilene is a type of stitch that has been traditionally used in cases of a suspected weak cervix because it's braided materials to offer better strength. In contrast Nylon is a single filament suture proposed to have the benefit of reducing infections which is considered to be one of the important reasons for preterm labour and probably stitch failure. Currently there is no evidence to support either of the sutures. We aim to find out whether the type of stitch makes any difference in preventing the preterm birth. To our knowledge COTS is the first study to address this issue.

Do I have to take part?
No. It is up to you to decide. The researcher will telephone you in the next few days to ask if you wish to take part. You will have an opportunity to go through this information leaflet with the researcher.

What will happen to me if I take part?

You will be asked to sign the consent form to show that you have agreed to take part. You are free to withdraw (change your mind) at any time, without a reason. This would not affect the care you receive.

There are 4 choices of participation in this study:

1. You would like to take part in the study(be randomized) and be contacted in the future for an interview about recruitment into the trial

2. You would like to be randomized but don't want to be contacted in the future for an interview about recruitment into the trial
3. You don't want to be randomized, but you are happy for us to subsequently retrieve data from your notes

4. You don't want to be randomized and you don't want us to review your notes

If you agree to participate you will be randomly (by chance) allocated to one of the two groups (Monofilament or Multifilament suture). The allocation to one of the groups will not affect the type of anaesthetic, the timing of the suture or future pregnancy management. We will then retrieve all other data from your notes. On agreement you will receive a further phone call to discuss your feelings about the study, as we also wish to investigate women's feelings and thoughts about being involved in research.
The stitch will be inserted under either general (you will be asleep) or regional anaesthetic (injection in the back) and you will therefore be awake. It is usually performed between the twelfth and sixteenth week of pregnancy.The length of time you will be in hospital depends on your consultant's instructions. However, you will probably go home the day after your operation. The cervical stitch is removed by a doctor at 37-38 weeks of pregnancy or when labour starts. The removal of the stitch does not usually require an anaesthetic. If you are going to have Elective Caesarean Section, then suture removal will be delayed until that time. When the stitch is removed, we will ask your permission to retain it for microbiological investigations.

What will happen if I chose not to take part?

Nothing. If you decide not to take part, please inform the researcher when (s)he telephones you. The researcher will not contact you again. This will not affect any care you receive from Birmingham Women's Hospital. If you were not in the study your doctor will still insert the stitch round the cervix using one of the above sutures dependent on their usual practise as part of your antenatal care.

What are the risks of taking part?

There are no additional risks associated with taking part in this research. The risks of any cerclage are described below.

Both stitches are commonly used and have theoretical advantage in preventing preterm labour or midtrimester loss. Inserting cervical stitch is a relatively common procedure. However, there are always risks to any surgical procedure. The uncommon risks (occur in 1 out of 100-1000) include bleeding, infection and pain. It is usual to experience some period like tummy pain afterwards. We can give you some painkillers if necessary. You may also have some slight vaginal bleeding. This should stop within a few days. If you have increased vaginal discharge and your doctor worried about the infection, you may have vaginal swab taken. If there is evidence of infection you may be prescribed antibiotics.
There is no evidence that abstinence from sex following cerclage insertion has any impact on preterm delivery. It is also not routinely recommended to get a complete bed rest after the procedure.

Appendix 5- Trial documents, Patient information leaflet, page 3

In a very small percentage of cases there is a technical difficulty with the procedure, so it may result in miscarriage or rupture of membranes. This is not, as far as we are aware, related to the suture material. The risk of premature delivery of the baby remains throughout the pregnancy (but this is the reason for the stitch).

What are the possible benefits of taking part?

There are no direct benefits to participants. The information we get from this study will help us to identify which suture is best to be used for the cerclage(stitch round the cervix) and is the best for prolongation of pregnancy.

Are there any contraindications to cerclage insertion?

Yes, there are. Cerclage cannot be performed if you have a signs of infection in your womb or in membranes round the baby, if you have continuing vaginal bleeding.

If you have any concerns?
If you have a concern about any aspect of this study, you should ask to speak to the researcher Dr F Israfilbayli on . If you wish to complain about the study, you can contact our Patient Information and Advice Centre (PAIC) on 0121 6272747.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you and your baby during the course of the research will be kept strictly confidential.

What will happen to the results of the research study?

We aim to publish the results in scientific journals. You will not be identified in any report or publication. Your personal details are not shared with anyone outside Birmingham Women's Hospital. A copy of the results will be offered to you at the end of the study.

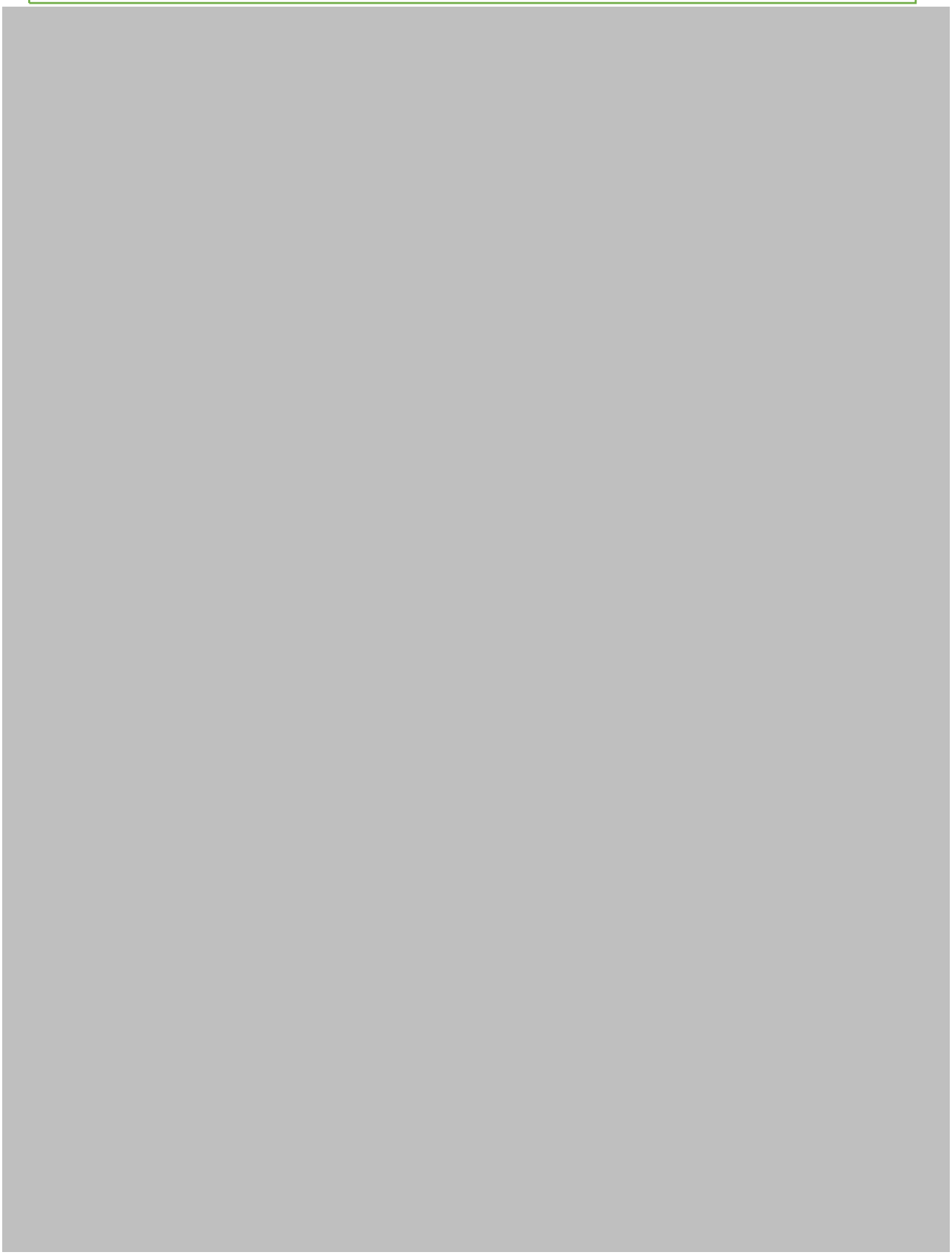
Who is organising and funding the research?
Study is funded by Birmingham Women's Hospital.

Who has reviewed the study?
Edgbaston Research Ethics Committee, Birmingham Clinical Trials Unit and Birmingham Women's Hospital Research and Development Committee have reviewed the study.

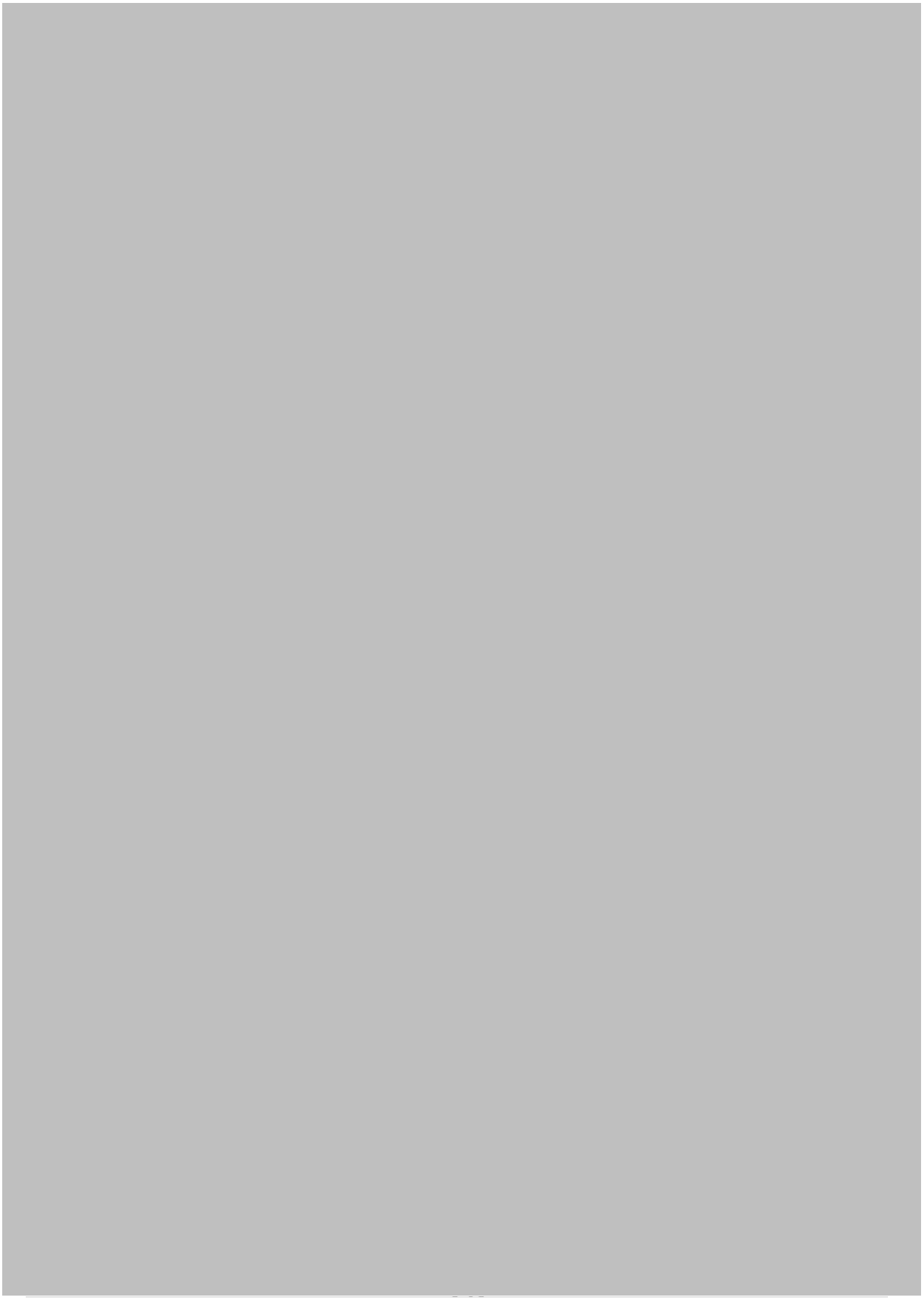
Contact for further information
If you want to know more about the study or there are any issues you would like to clarify please contact: Fidan Israfilbayli

Thank you for taking time to read this leaflet. We hope that you will be willing to help us with this study.

Appendix 6- Ethical approval letter, page 1

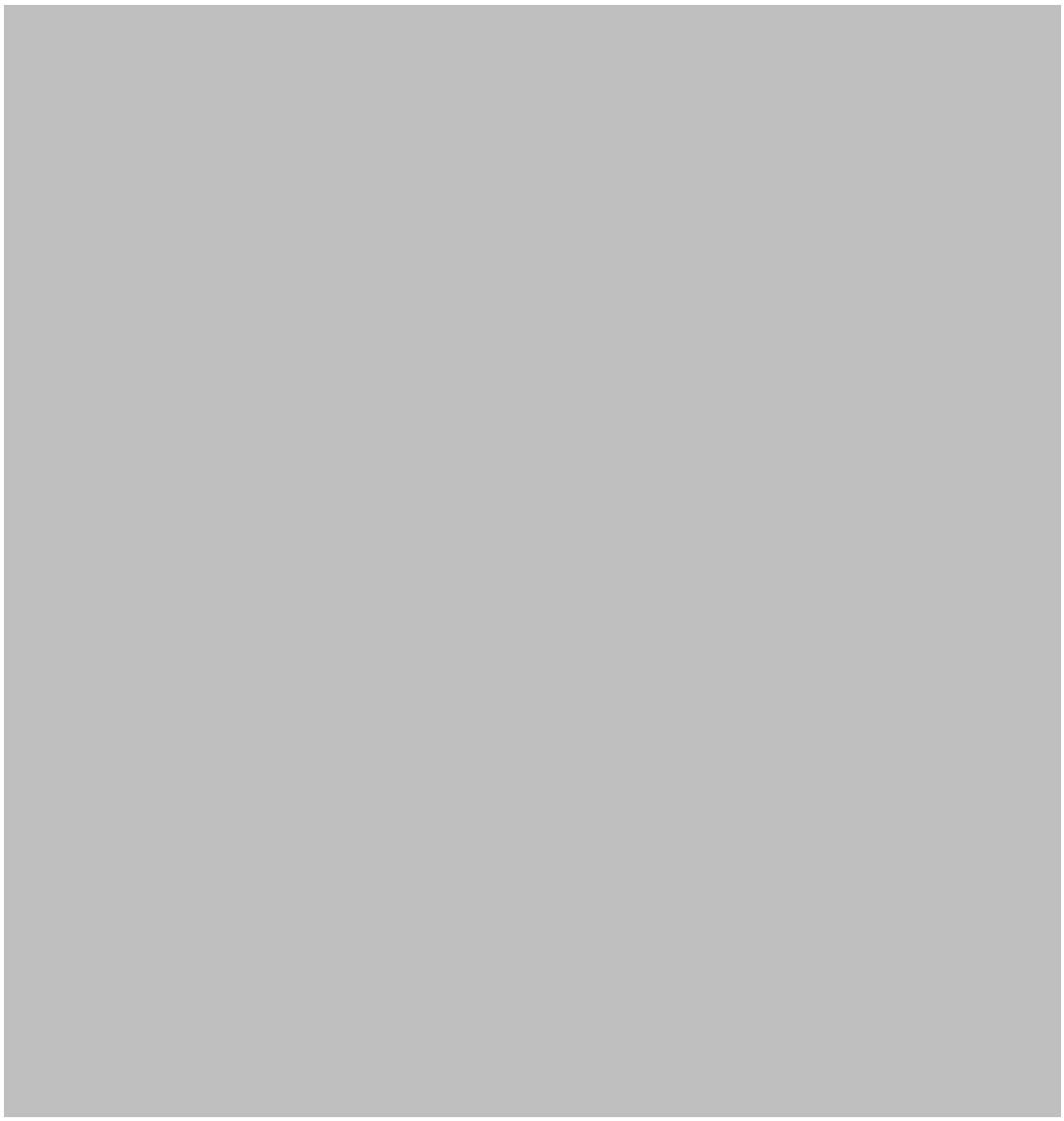


Appendix 6- Ethical approval letter, page 2

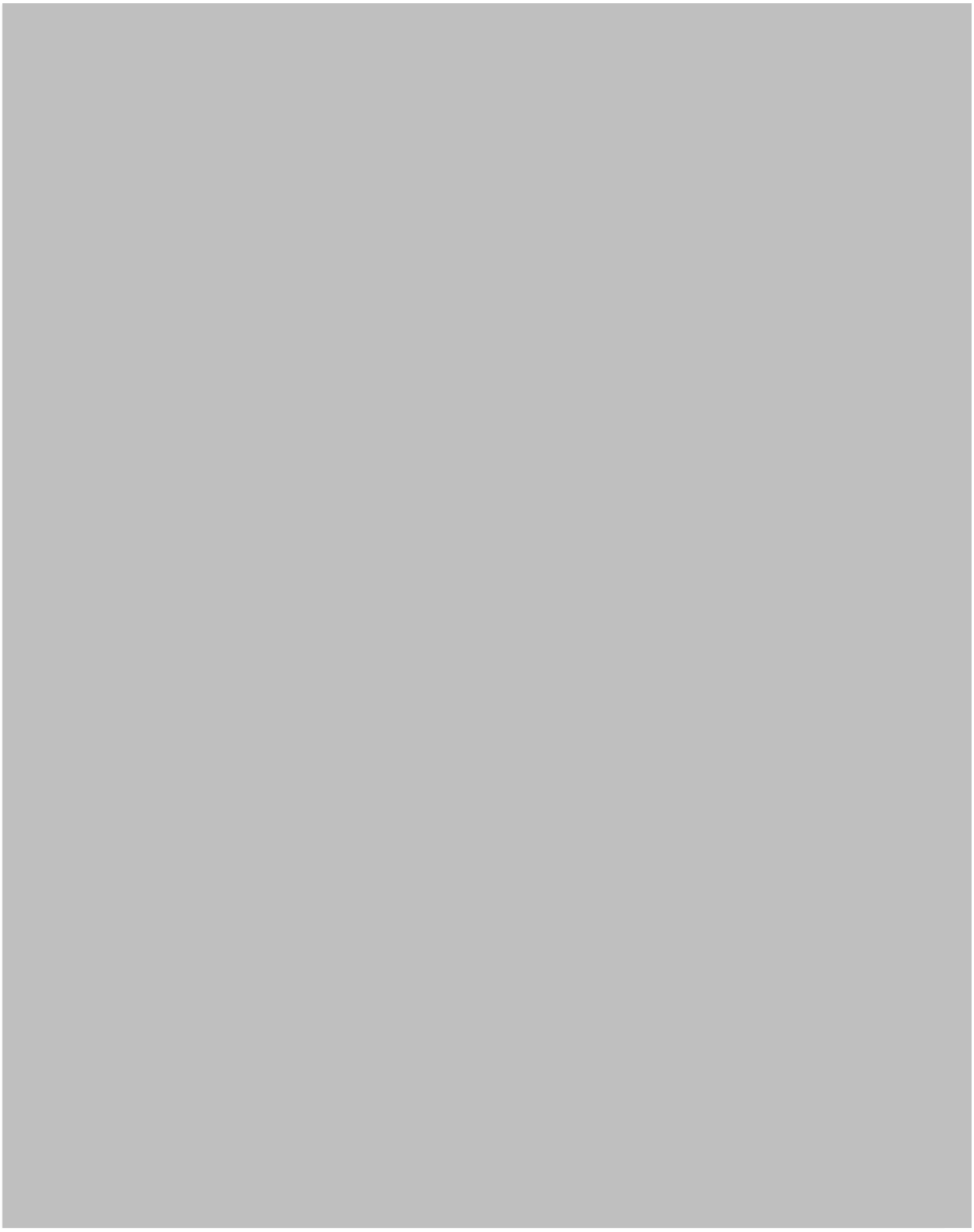


Appendix 6 - Ethical approval letter, page 3

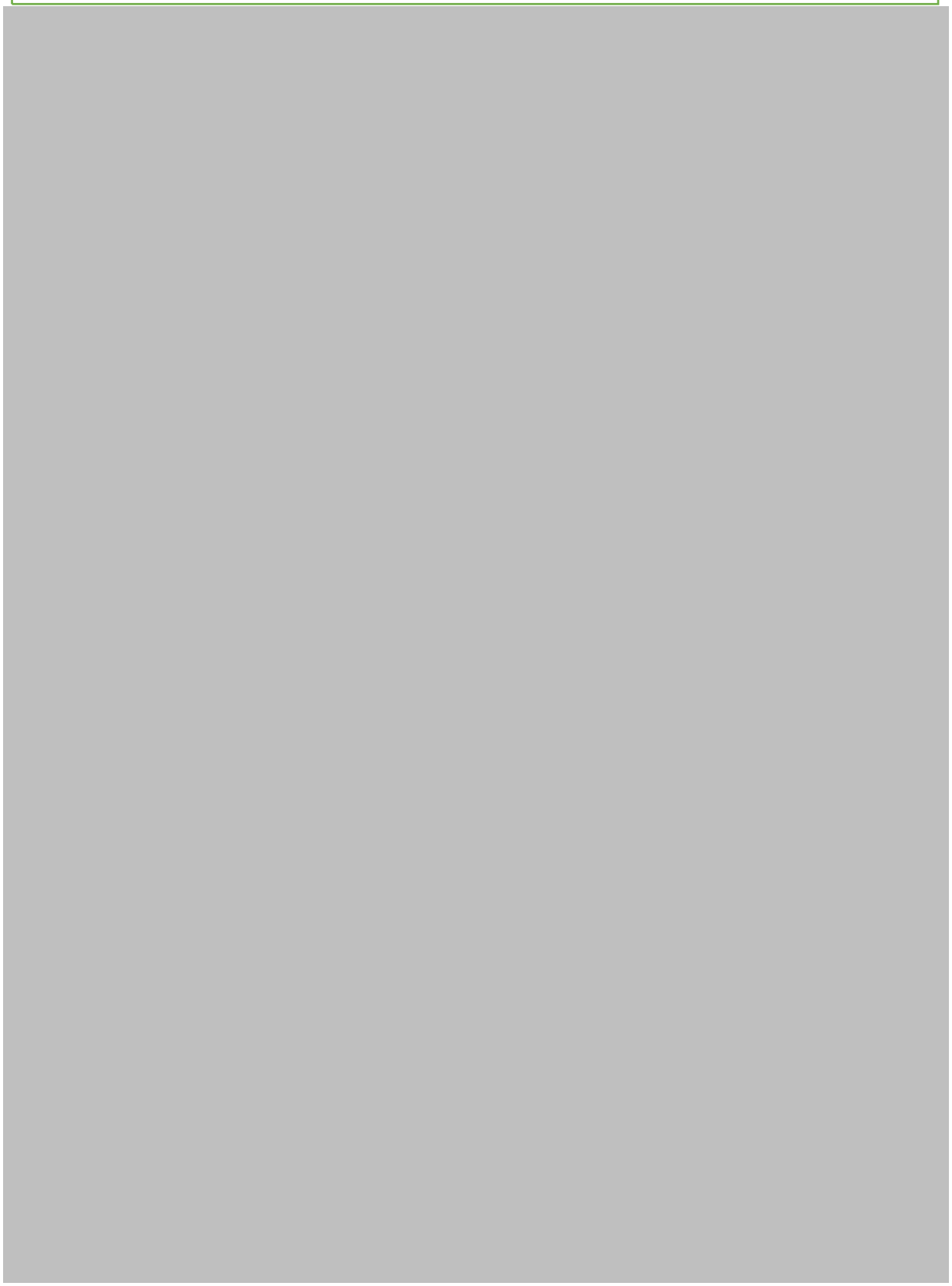
Appendix 7- BCTU letter of support



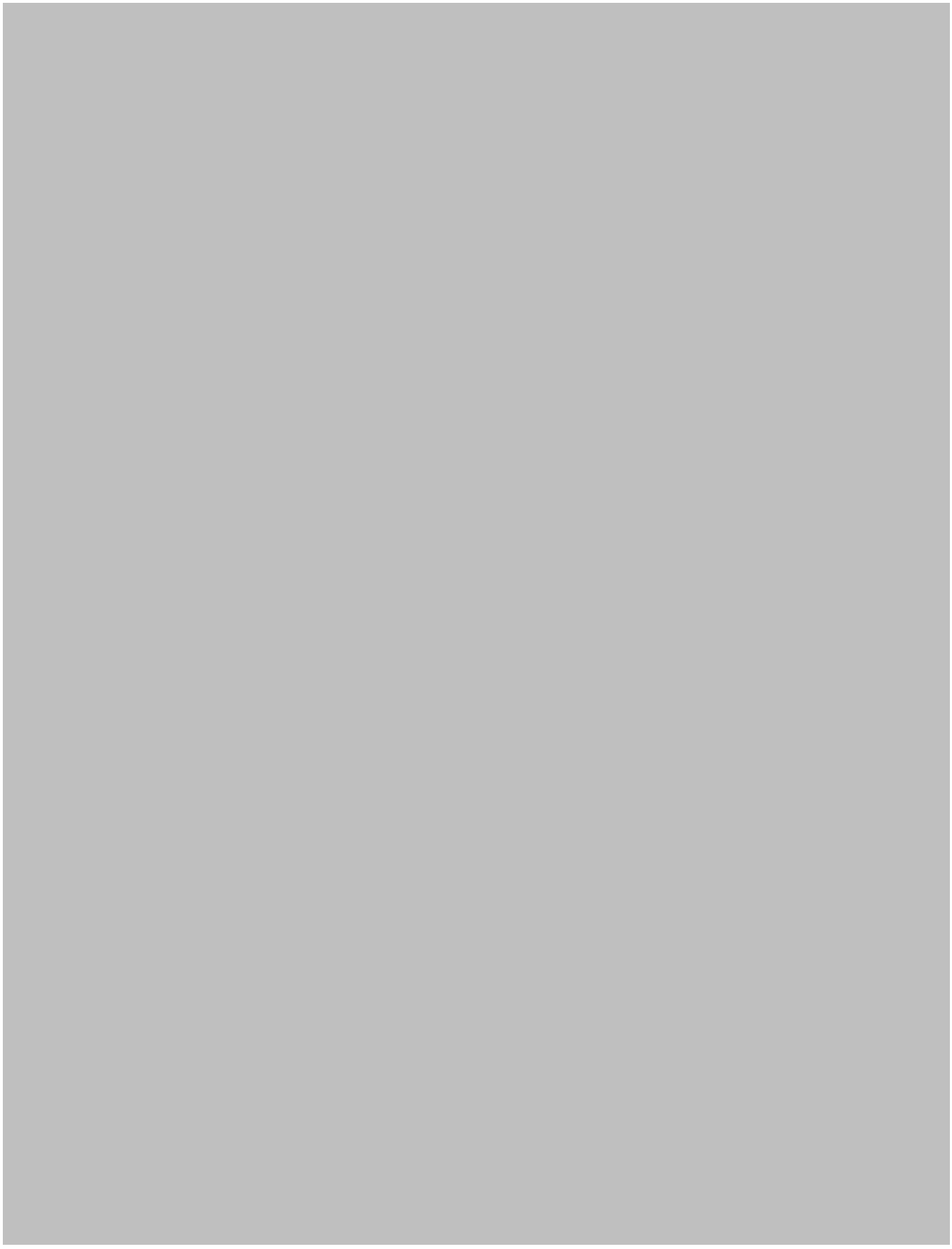
Appendix 8 - RfPB outcome letter 1



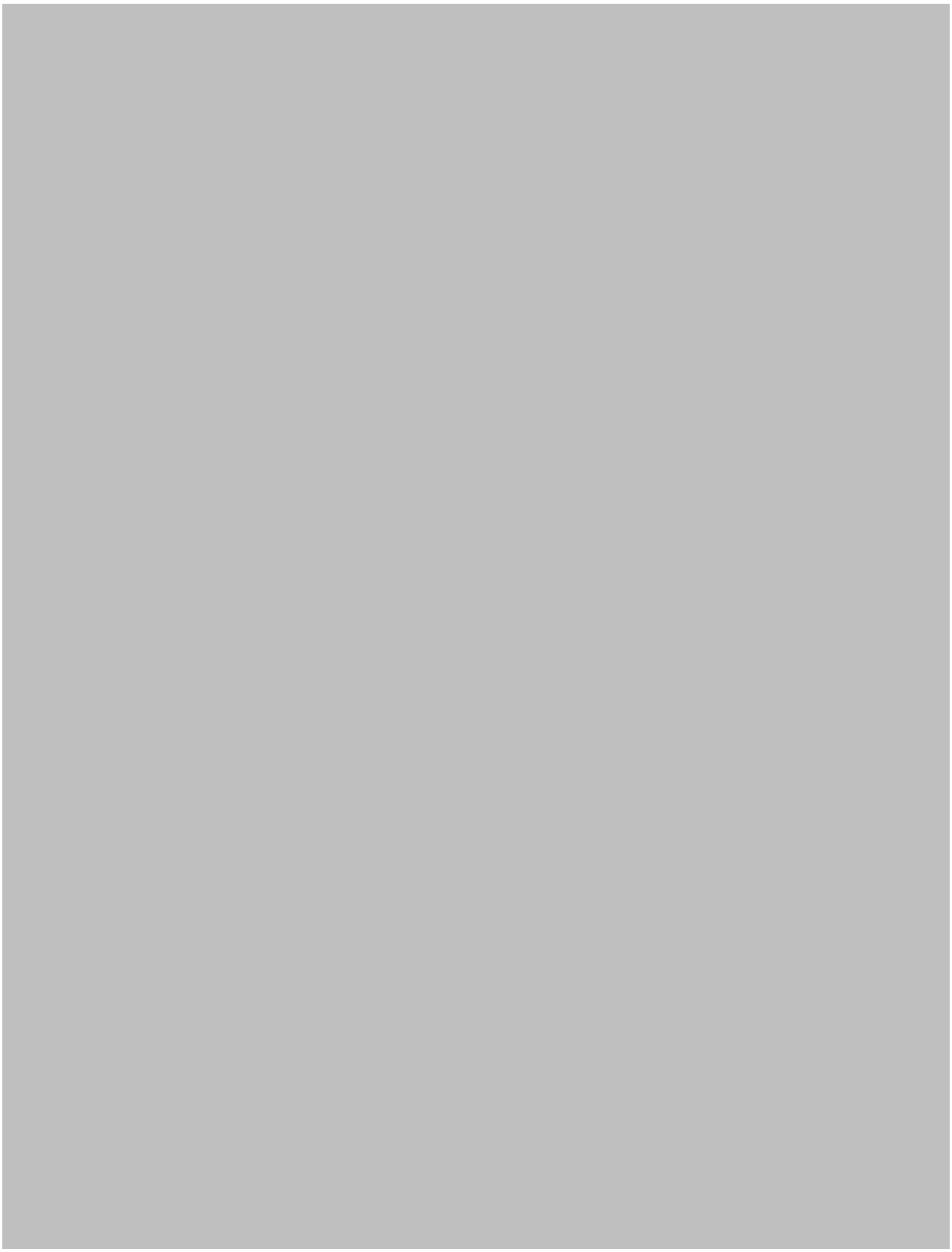
Appendix 8- RfPB outcome letter 2



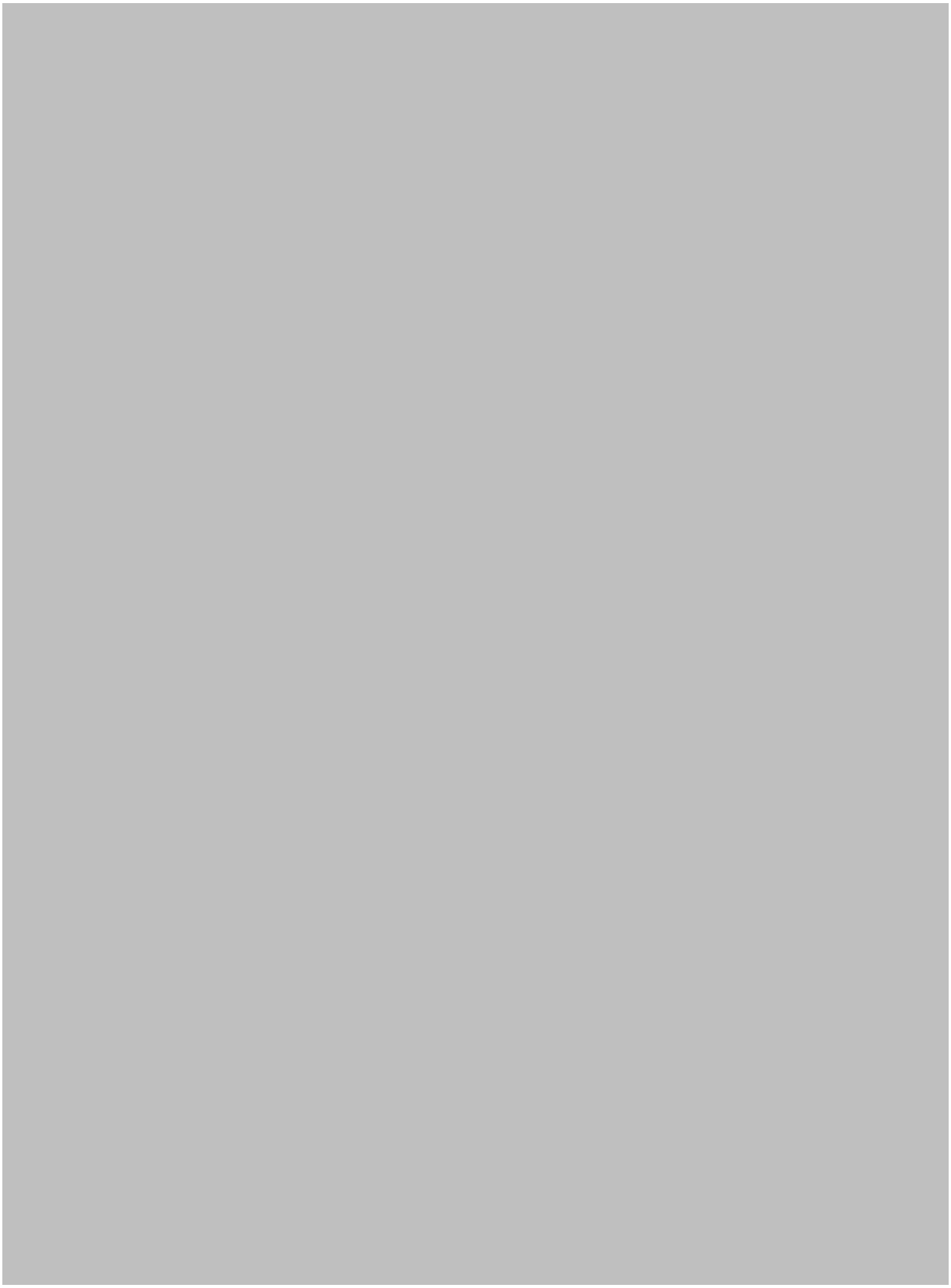
Appendix 9- RfPB lay review form, page 1



Appendix 9- RfPB lay review form, page 2

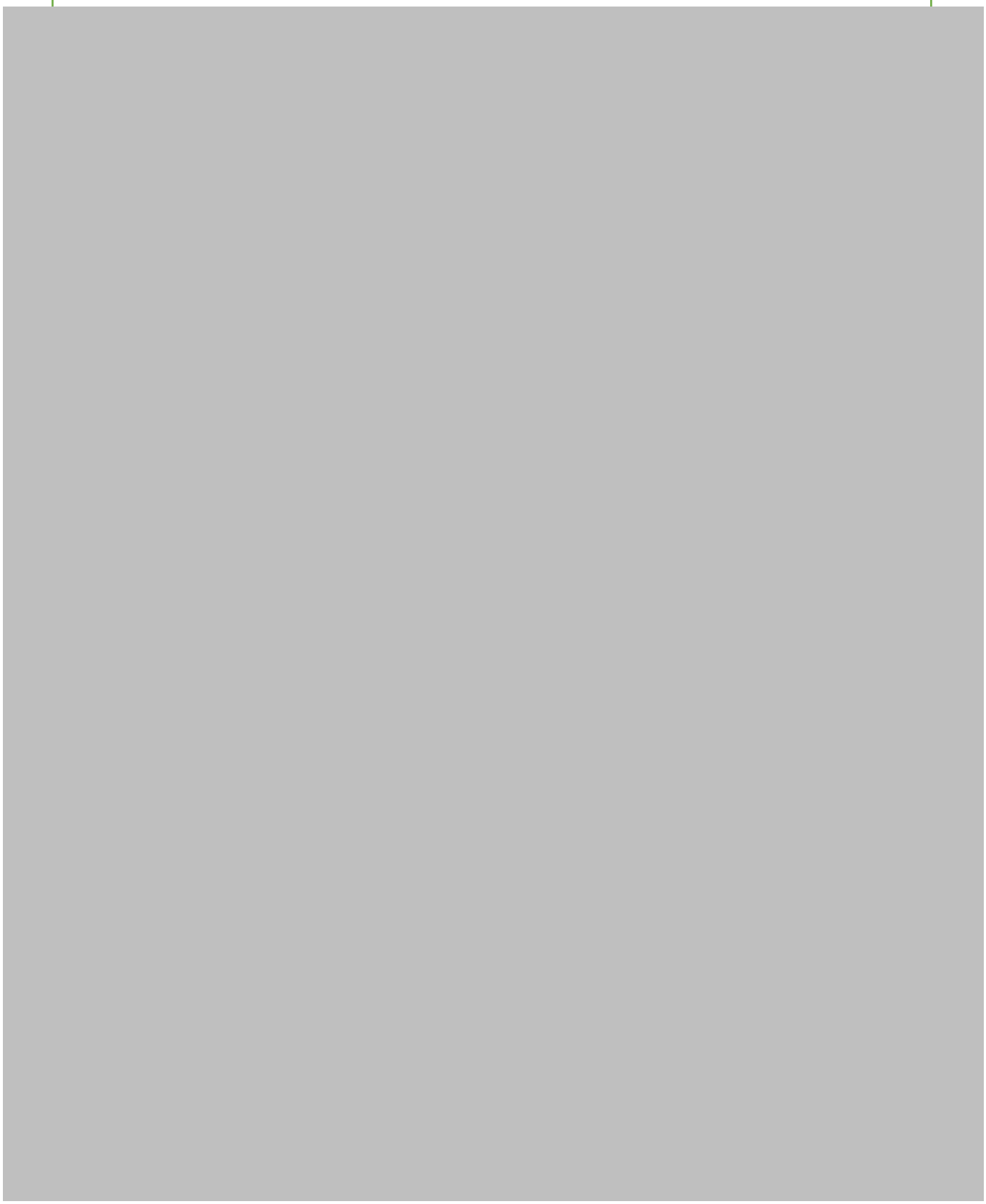


Appendix 9- RfPB lay review form, page 3

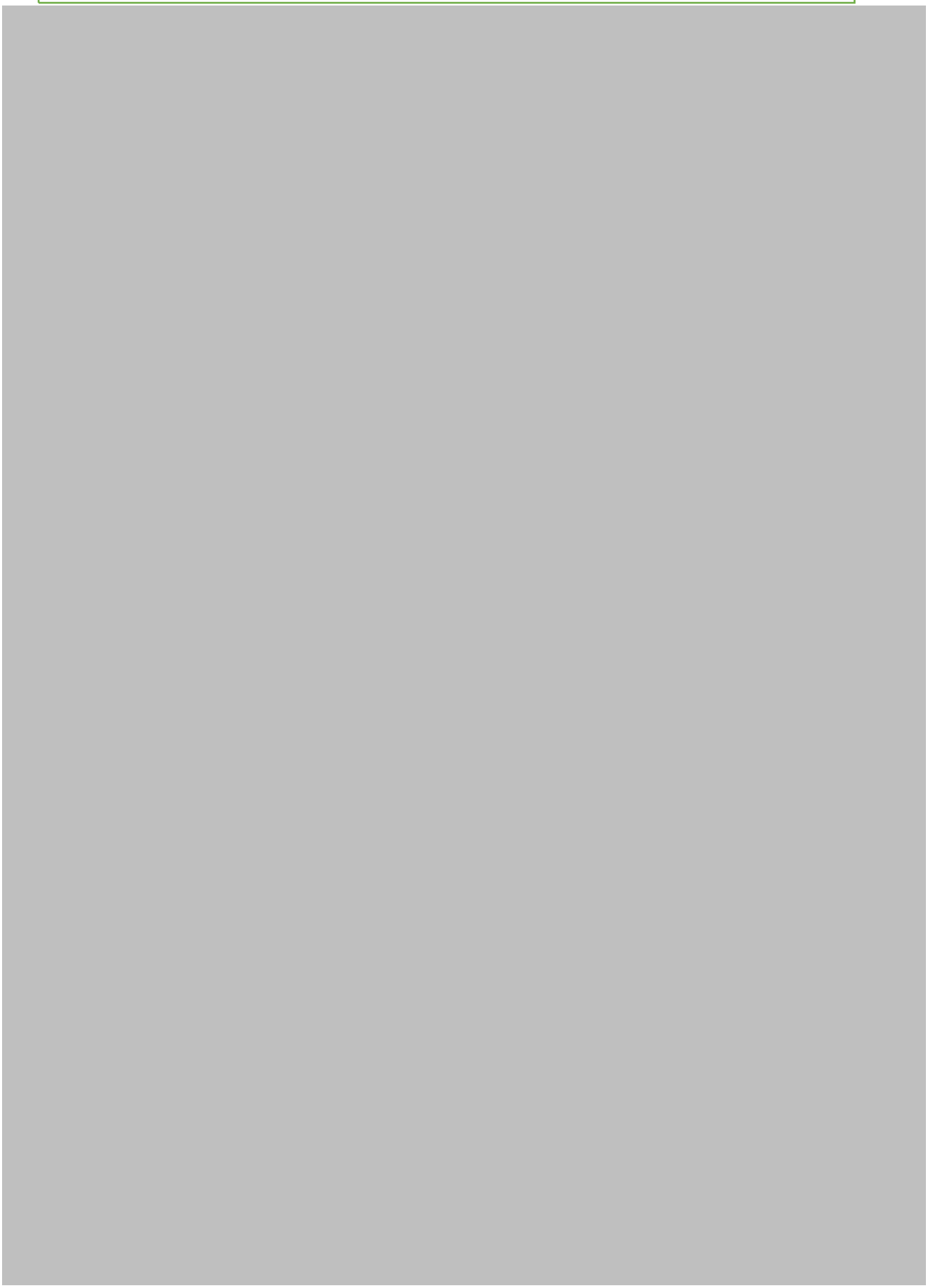


Appendix 9- RfPB lay review form, page 4

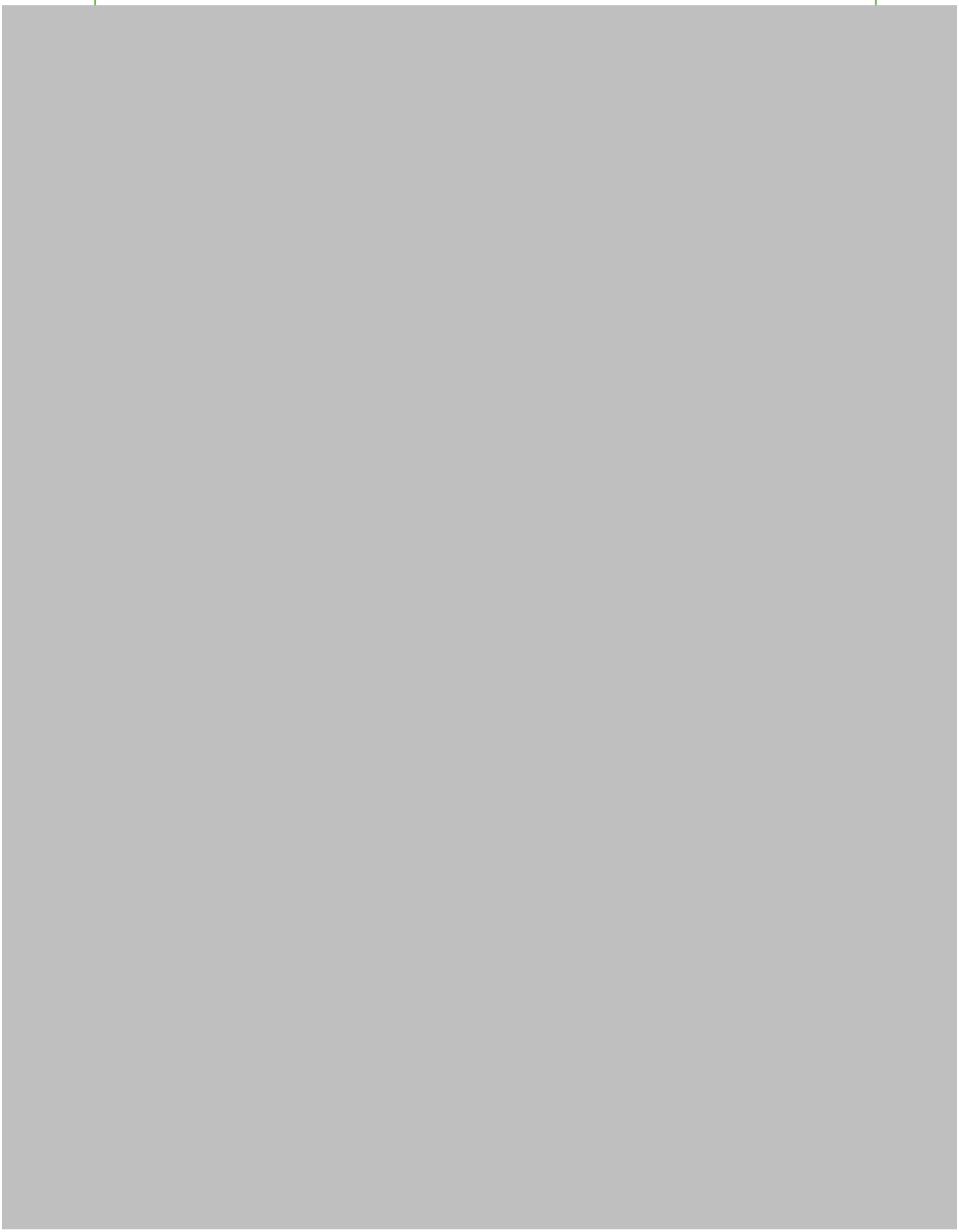
Appendix 10- PRIME group meeting agenda



Appendix 11, Minutes from groups supporting COTS study, page 1



Appendix 11, Minutes from groups supporting COTS study, page 2

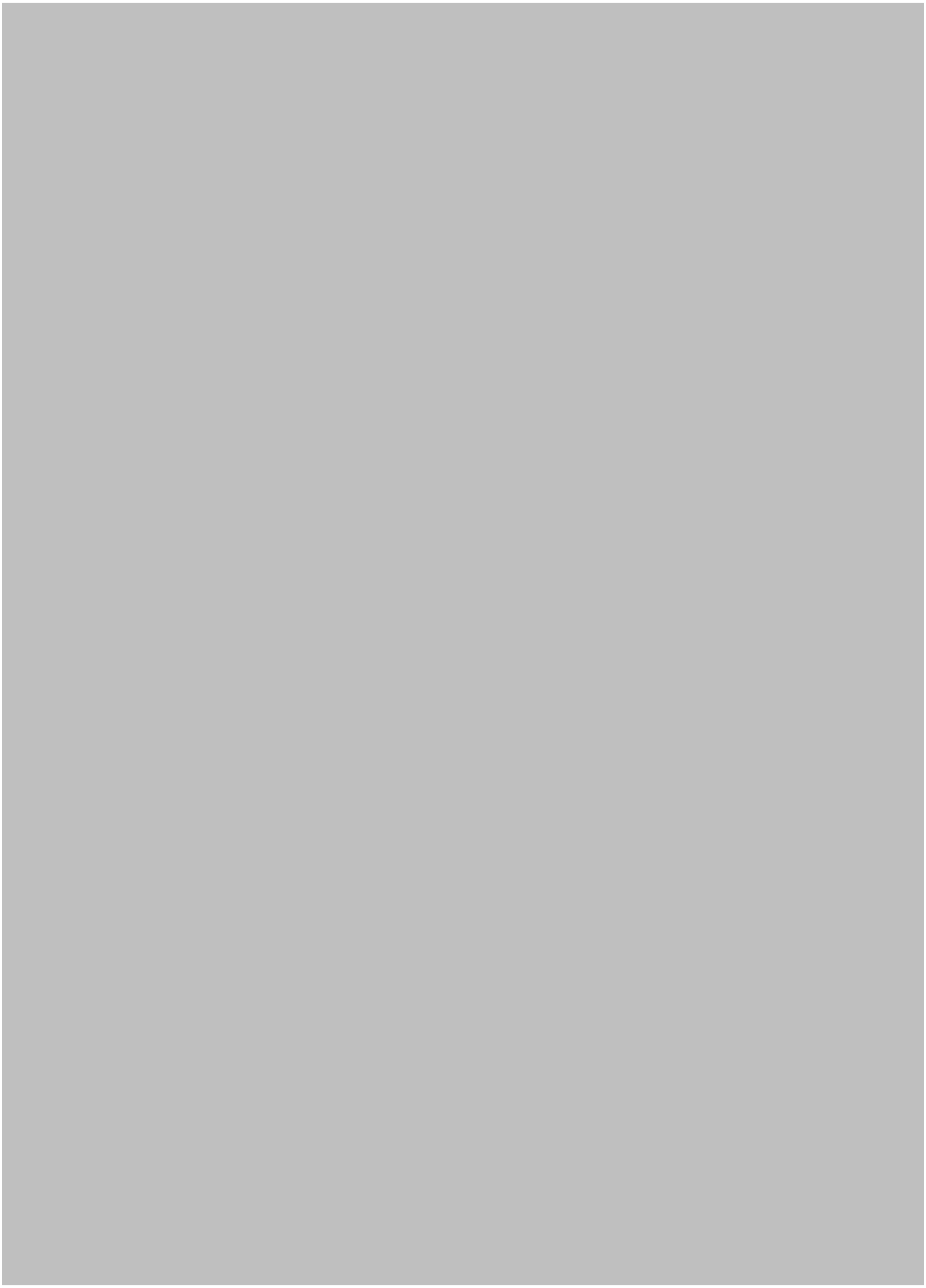


Appendix 11, Minutes from groups supporting COTS study, page 3

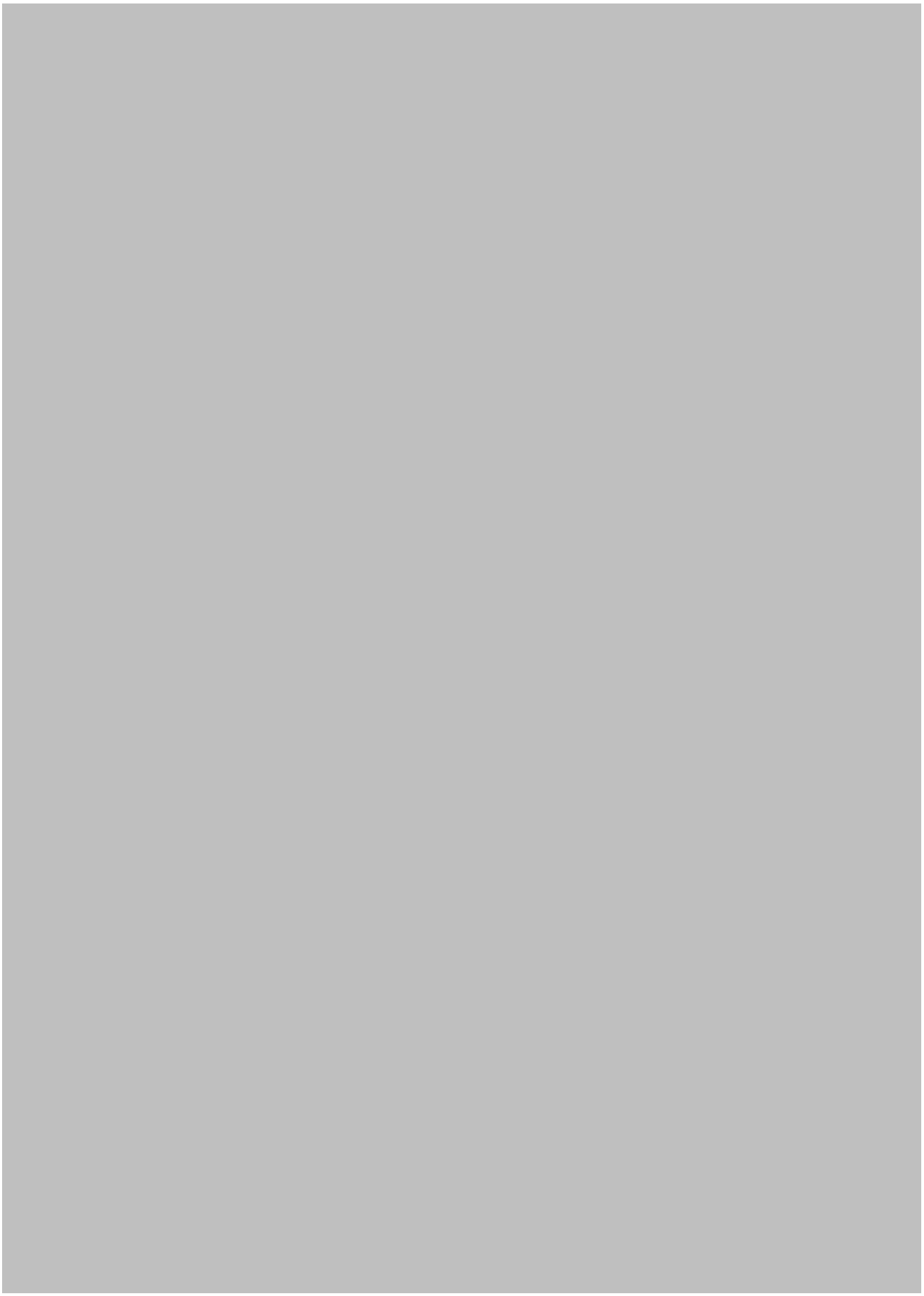
Appendix 12, Lay summary

COTS study addresses a research question, which could potentially save the lives of more than 400 babies per year in the UK alone. These babies would otherwise die because of severe prematurity or early pregnancy loss. Undoubtedly, the improved outcome will have significant psychosocial benefits and health resource implications.
Laxity of the neck of the womb (cervix) is one of the main causes of premature birth and early pregnancy loss for which a suture around the cervix (cerclage) has been used for many years. It is estimated that 6700 women will have a cerclage in the UK / year with varying success rates. Braided sutures have been traditionally used because they are deemed to be strong and easy to remove. However, braided non-dissolvable sutures have been consistently associated with increased risk of infection in most surgical procedures and are no longer used in eye and pelvic surgery for that reason. Infection is a major contributing factor to cerclage failure. Hence, some surgeons prefer to use monofilament non-braided sutures in cerclage. However, there is perceived concern about the degree of cervical support such sutures offer. We conducted a national survey of UK-based consultants Obstetricians & Gynaecologists which demonstrated that the majority of doctors were uncertain which is the best suture material for their patients. Therefore, COTS pilot study will provide the necessary information to confidently inform the need for a large national multi-centre study.

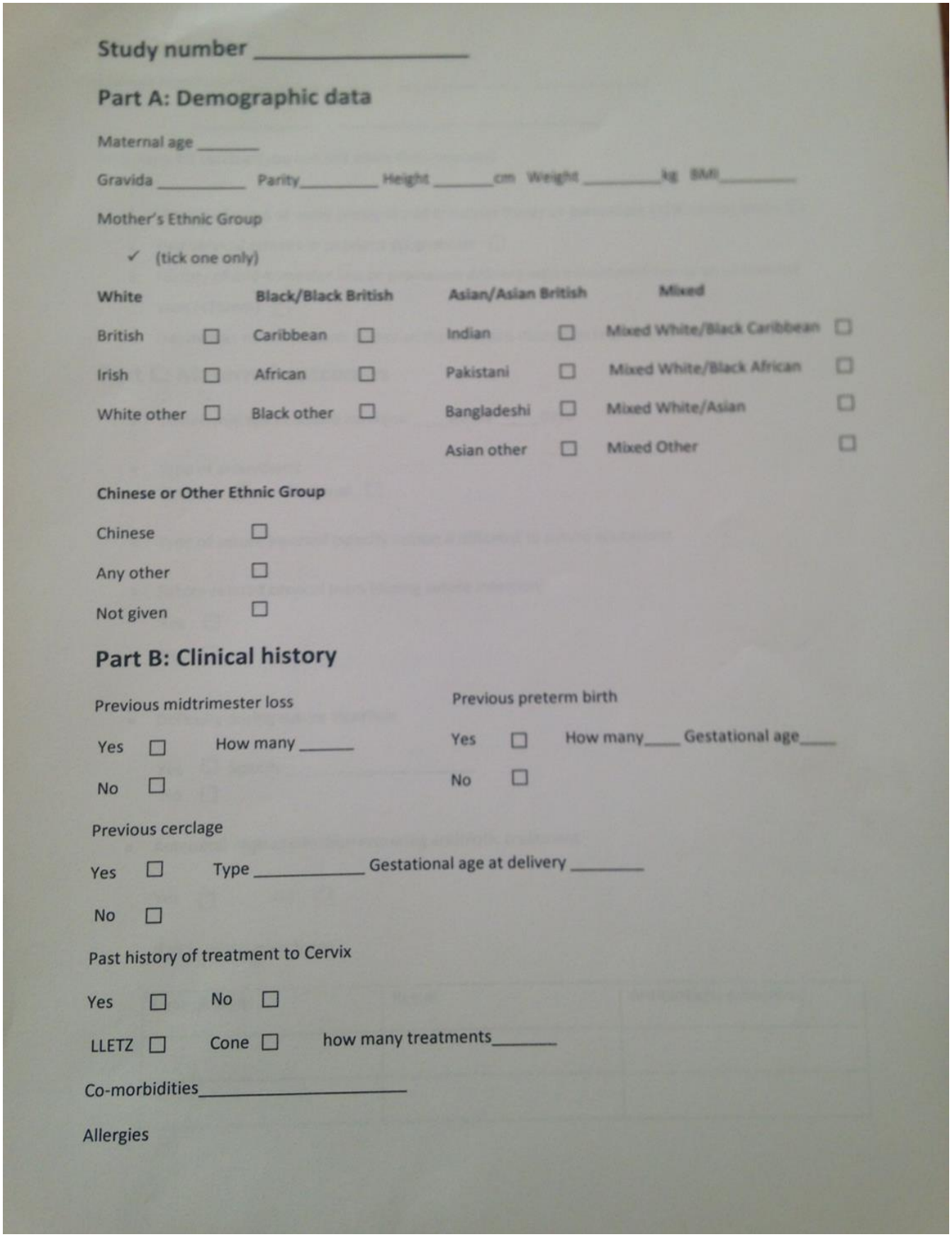
Appendix 13, Letter of access 1



Appendix 13, Letter of access 2



Appendix 14 – Outcome data collection form, page 1



Study number _____

Part A: Demographic data

Maternal age _____

Gravida _____ Parity _____ Height _____cm Weight _____kg BMI _____

Mother's Ethnic Group

✓ (tick one only)

White		Black/Black British		Asian/Asian British		Mixed	
British	☐	Caribbean	☐	Indian	☐	Mixed White/Black Caribbean	☐
Irish	☐	African	☐	Pakistani	☐	Mixed White/Black African	☐
White other	☐	Black other	☐	Bangladeshi	☐	Mixed White/Asian	☐
				Asian other	☐	Mixed Other	☐

Chinese or Other Ethnic Group

Chinese ☐

Any other ☐

Not given ☐

Part B: Clinical history

Previous midtrimester loss

Yes ☐ How many _____

No ☐

Previous preterm birth

Yes ☐ How many____ Gestational age____

No ☐

Previous cerclage

Yes ☐ Type _____ Gestational age at delivery _____

No ☐

Past history of treatment to Cervix

Yes ☐ No ☐

LLETZ ☐ Cone ☐ how many treatments_____

Co-morbidities_____

Allergies

Appendix 14 – Outcome data collection form, page 2

Yes ☐ No ☐

Current Medications _____ _____ _____

_____ _____ _____

Indication for cerclage(you can tick more then one box)

1. History of three or more previous mid trimester losses or premature (<28 weeks) births ☐
2. Had cervical sutures in previous pregnancies ☐
3. History of mid-trimester loss or premature delivery with a shortened cervix on ultrasound scan (<25mm) ☐
4. Deemed at risk of preterm labour at the clinicians discretion (e.g. radical trachelectomy) ☐

Part C: Maternal outcomes

- Gestational age at suture insertion ____weeks _____days
- Type of anaesthetic
  General ☐ Regional ☐
- Type of suture inserted (specify reason if different to suture allocation)
- Suture-related cervical tears (during suture insertion)
  Yes ☐
  No ☐
- Difficulty during suture insertion
  Yes ☐ Specify _____
  No ☐
- Antenatal vaginal infection requiring antibiotic treatment
  Yes ☐ No ☐
  If YES, give details here:

Date of swab	Result	Antibiotic(s) prescribed

Appendix 14 – Outcome data collection form, page 3

- Maternal side effects other than infection

  vaginal discharge ☐

  bleeding ☐

  pyrexia not requiring antibiotics ☐

- Chorioamnionitis requiring suture removal and delivery

  Yes ☐ Confirmed microbiologically _____

- Mode of delivery

  Vaginal birth ☐

  Caesarean section

  Elective ☐

  Emergency ☐

- Gestational age at delivery ____weeks _____days

- Gestational age at suture removal ____weeks _____days

- Difficulty of suture removal: yes ☐ no ☐

- Reason for suture removal

  SROM ☐ PTL ☐ infection ☐ routine ☐ other (specify) ☐_____

Part D: Fetal / Neonatal outcomes

- Pregnancy loss:

  Yes ☐ miscarriage ☐ IUD ☐ NND within 7 days ☐ NND after 7 days ☐

  No ☐

  Preterm birth :

  28+1/40- 32/40 ☐

  32+1/40- 34/40 ☐

  34+1/40- 37/40 ☐

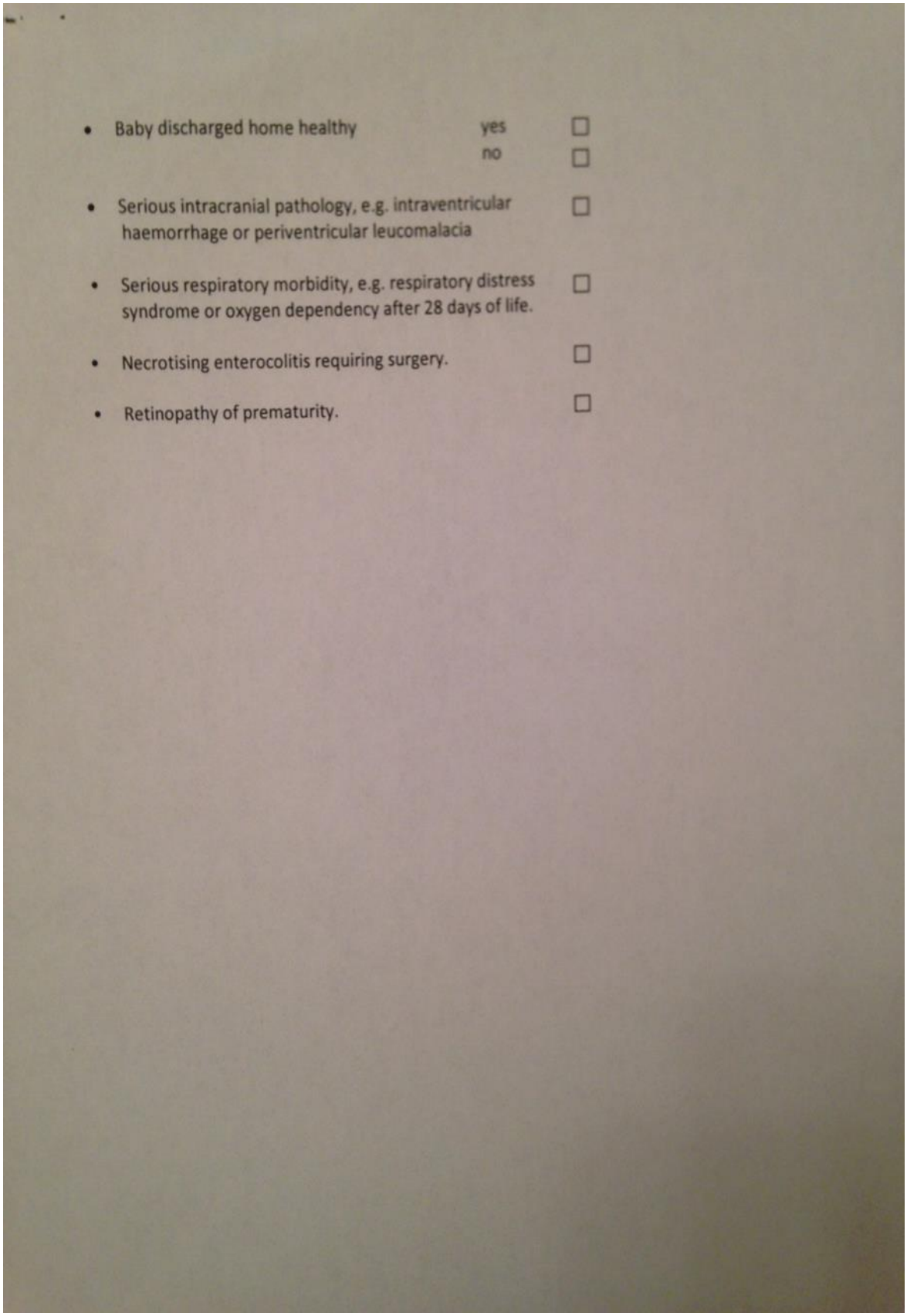
- Gestational age at birth _____

- Cord gases A: _____

  V: _____ N/A _____

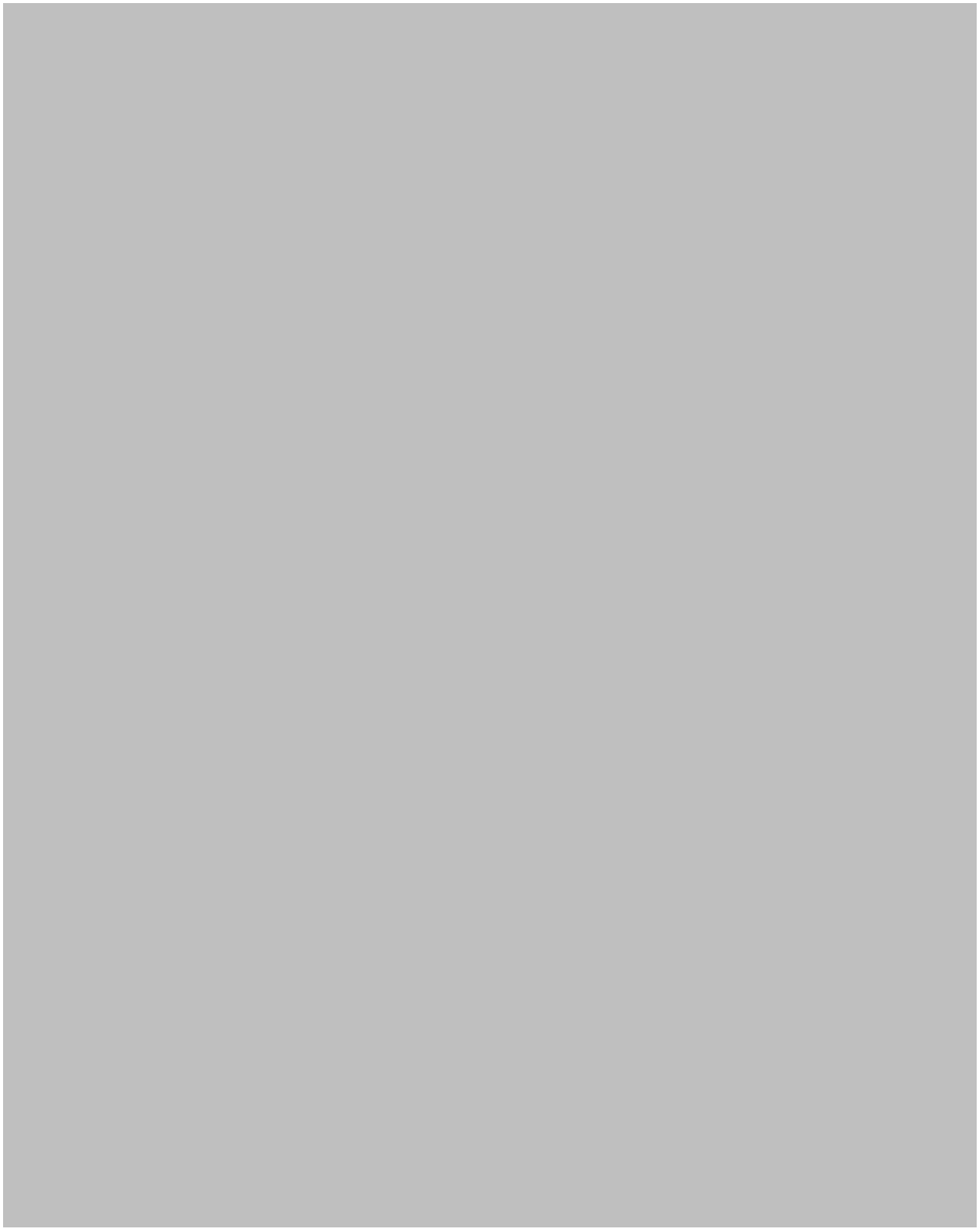
- APGAR score 1 min _____ 5 min _____ N/A_____
- Days in neonatal unit _____ days N/A _____

Appendix 14 – Outcome data collection form, page 4



- Baby discharged home healthy — yes ☐ / no ☐
- Serious intracranial pathology, e.g. intraventricular haemorrhage or periventricular leucomalacia ☐
- Serious respiratory morbidity, e.g. respiratory distress syndrome or oxygen dependency after 28 days of life. ☐
- Necrotising enterocolitis requiring surgery. ☐
- Retinopathy of prematurity. ☐

Appendix 15 -Declaration of end of study form



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