CERM Trial Protocol

Short title	The CERM trial
Full title	Chronic Endometritis and Recurrent Miscarriage - The CERM trial
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Protocol Amendments

Amendment No.	Date of Amendment	Date of Approval
X	dd/mm/yyyy	dd/mm/yyyy
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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/199828) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's and Warwick Clinical Trials SOPs and other regulatory requirements as amended.

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

For and on behalf of the trial Sponsor:

Name	Signature	Position	Date
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Professor Siobhan Quenby		Professor of Obstetrics	21 June 2019
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Table 4 –Trial Management Team Information

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TRIAL SUMMARY

Item	Details
Trial title	Chronic Endometritis and Recurrent Miscarriage - The CERM trial
Short title	The CERM trial
Trial aim	The aim of this trial is to determine if doxycycline administered prior to conception improves pregnancy outcome in women with recurrent miscarriage associated with chronic endometritis (CE) and explore the mechanisms by which it could prevent miscarriage.
Clinical phase	Phase II/III trial
Trial design	A prospective, multi-centre, randomised, double blind adaptive designed trial, comparing a course of doxycycline against placebo.
Trial participants	Women who have experienced two or more consecutive first trimester miscarriages, who are aged ≥18 to <42.
Trial arms	**Intervention arm** – 100mg of doxycycline twice daily for 14 days. **Control arm** – placebo twice daily for 14 days.
Planned sample size	Sample size for endometrial biopsy N=3,062. Sample size for women who screen positive for CE and wish to enter the randomised controlled trial n=1,500, n=750 in the intervention arm (doxycycline) and n=750 in the control arm (placebo). This trial will use adaptive design methodology so the trial can stop early, with fewer than 1500 patients randomised, in the case of better than expected efficacy or in the case of futility.
Planned trial period	48 months
Treatment duration	Women who screen positive for CE will take the doxycycline/placebo for 14 days.
Follow-up duration	Women without CE • All women will remain in the trial until delivery or pregnancy demise or for 12 months after result of the biopsy or the trial ends. Women with CE recruited into randomised control trial • If women have a pregnancy demise before 24 weeks gestation they will remain within the trial and successive pregnancies recorded and monitored as part of trial outcomes. • All women will remain in the trial until six - eight weeks post-delivery or pregnancy outcome (if gestation >24 weeks) or the trial ends.
Planned recruitment start date	01/10/2019 **Planned trial end date** 01/05/2023
	Objectives **Outcome Measures**

Primary	To find out if doxycycline given prior to conception improves the number of on-going pregnancies and total live births in women with recurrent miscarriage associated with chronic endometritis?	**Primary Outcome 1** • On-going pregnancy at 12 weeks **Primary Outcome 2** • Total live births
Secondary	To find out if doxycycline treatment improves CE? To examine the separate effects of doxycycline on conception, early miscarriage, and late miscarriage. In addition assess the mediation effect of each of these, on the primary outcome, with treatment effect as a covariate.	Density of CD138+ cells in the endometrium before and after treatment with doxycycline/placebo. Time to first conception Anticipated time to first live birth The proportion of women with a live birth after 24 weeks of gestation in their first pregnancy after randomisation. Pregnancy complications Early pregnancy complications Type of miscarriage On-going pregnancy and live births per patient in women excluded from randomisation by having low CD138+ cell scores and those randomised to placebo.
Exploratory	To find out if doxycycline treatment changes Lactobacillus-deplete microbiota to a Lactobacillus-dominated microbiota? To find out if doxycycline treatment, improves the differentiation potential and colony-forming activity of endometrial stromal cells? To find out if CE is related to heightened senescence of endometrial stromal cells?	Evaluate changes of Lactobacillus-deplete microbiota to a Lactobacillus-dominated microbiota after treatment with doxycycline/placebo. Assess changes in differentiation potential and colony-forming activity of endometrial stromal cells after treatment with doxycycline/placebo. Assess senescence associated β Galactosidase activity in patients with CE.
IMP	Doxycycline, an antibiotic available on prescription and used for the treatment of infections caused by bacteria and parasites.	

Formulation, dose, route of administration	**Doxycycline Capsules** **Dose:** 100 mg twice a day **Route:** oral **Duration:** 14 days	**Placebo Capsules** **Dose:** twice a day **Route:** oral **Duration:** 14 days
Key words	Chronic Endometritis; Recurrent Miscarriage; Microbiome; RCT; Doxycycline.	

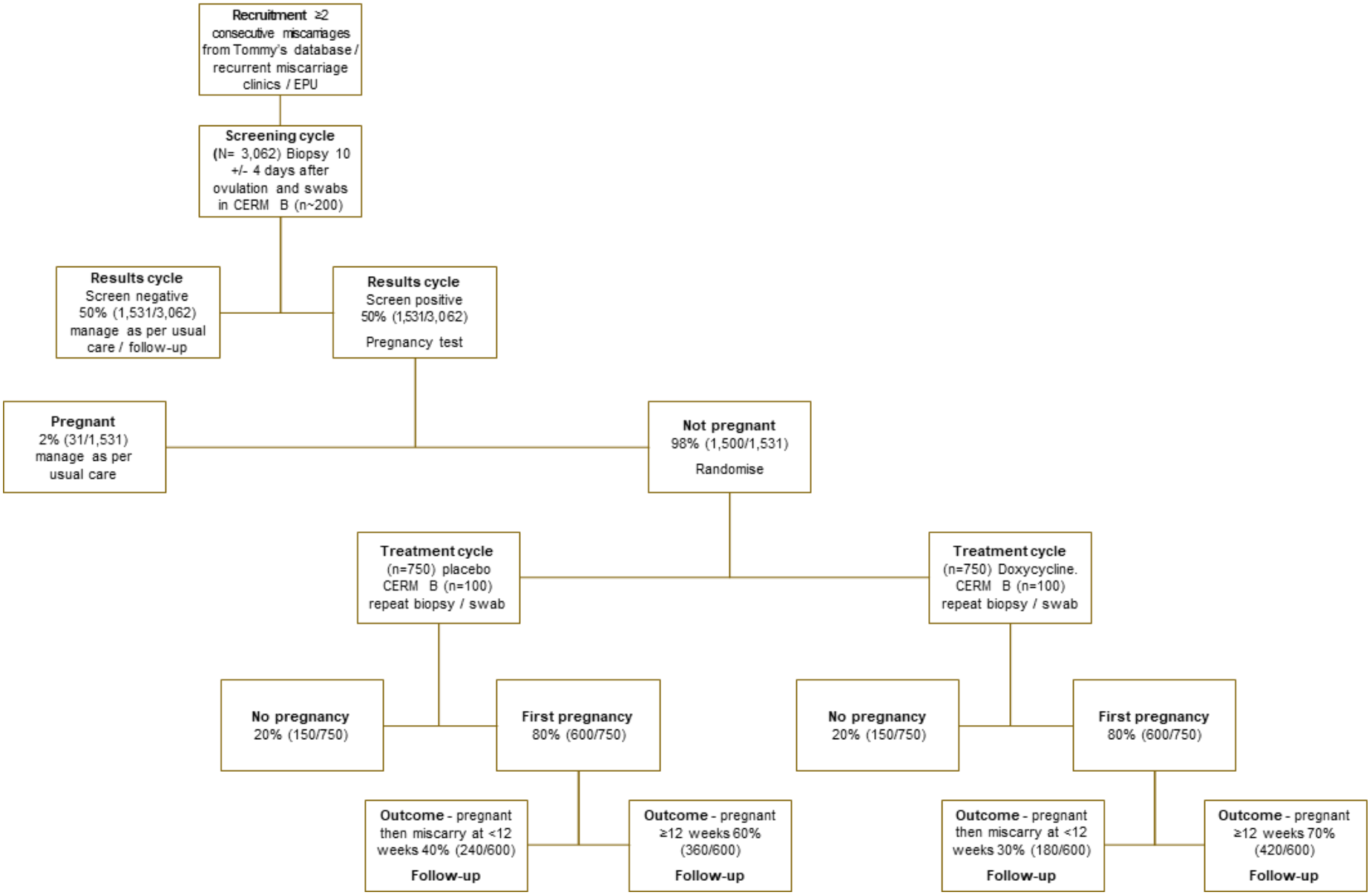

Figure 1 – CERM Process Flowchart

Table 5 – CERM Schedule of Events

Observations/Procedures		Registration		Randomisation	Post-treatment	Pregnancy	Main RCT Trial Assessments			
	Tommy's NET/RM Clinic/EPU	Pre-reg	Post-reg	CE + women	Treatment completion	Pregnancy Review	12 (+/- 2) weeks[6]	20 -24 weeks[6]	Extra Scan[5]	End of pregnancy (6-8 wks)
CERM letter and PIS posted	●									
Telephone contact – Trial Participation	●									
Pre-screening eligibility	●									
Verbal Consent[1]	●									
Biopsy preparation kit sent/given	●				●[3]					
Patient Demographics		●								
BMI (Height/weight)		●								
Smoking history		●								
Medical History		●								
Concomitant medication review		●		●						
Obstetric History		●								
Pregnancy History		●								
Review Eligibility		●		●						
Pregnancy Test		●		●	●[3]					
Contraception use review		●		●	●					
Period Review		●		●	●[3]					
Written Consent Screening CERM A or CERM B[3]		●								
Registration		●								
Endometrial Biopsy			●		●[3]					
Swabs – CERM B Only[3]			●[3]		●[3]					
Inform patient of CE results			●							
Adverse event review				●	●	●				
Written Consent Randomisation[2]				●						
Randomisation				●						
Treatment instructions				●						
Dispense medication				●						

Treatment compliance check					●					
Contact patient every 3 months to determine pregnancy						●				
Pregnancy confirmation							●	●[4]		
Ultrasound							●	●	●[5]	
Concomitant medication review (on trial)					●		●	●	●	●
Pregnancy complications[4]							●	●	●	●
Pregnancy outcome assessments										●

[1] Verbal consent must be given (and documented) prior to biopsy kits being given/sent

[2]Written informed consent must be given prior to any trial specific procedures taking place.

[3]CERM B patients only (UHCW ONLY)

[4] If appropriate

[5]Only if clinically indicated

[6]Timing of visit as per local hospital policy

Table 6 – Trial tasks and Milestones

Tasks	Time period (months)
Trial preparation: approvals (ethics, R&D), research governance (oversight committees (TMG, TSC and DMC), staff training), develop project management plan, registration, contracting, new appointments, send capacity and capability questionnaires to trial sites, trial administration processes (participant files, master file), trial branding, and social media.	-2 - -1 (pre-start)
Trial set-up: liaise with trial pilot sites, track R&D, develop randomisation service, develop data collection process, prepare training manual, print recruitment information (introduction letter, participant information sheet, participant information leaflet, posters) and prepare site-initiation materials.	1 - 3
Site set-up: Initially ten sites; four per month (not including the first and last months, August and December).	4 - 22
Participant recruitment: n=1,500 randomised	5 -30
Feasibility: after six months when **>68** participants have been recruited.	Around 10
Follow-up: birth.	7 - 38
Interim analysis: when data on primary outcome on n=250, 500, 750, 1,000 available.	Around 9-21
Data analysis	36 - 40
Dissemination: final report, publications, press release, social media, newsletter and a dissemination event.	38 - 42

ABBREVIATIONS / GLOSSARY

Abbreviation	Description
AE	Adverse Event
AEPU	Association of Early Pregnancy Units
ART	Assisted Reproduction Techniques
CE	Chronic Endometritis
CI	Confidence Interval
CONSORT	Consolidated Standards Of Reporting Trials
CRF	Case Report Form
CRL	Crown-Rump Length
CSRL	Clinical Sciences Research Laboratories
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTIMPS	Clinical Trial of an Investigational Medicinal Products
DMC	Data Monitoring Committee
EME	Efficacy and Mechanism Evaluation
EnSCs	Endometrial Stromal Cells
EPU	Early Pregnancy Unit
EudraCT	European drug regulatory affairs Clinical Trials
ESHRE	European Society of Human Reproduction and Embryology
FBC	Full Blood Count
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
GP	General Practitioner
H&E	Haematoxylin and Eosin
HRA	Health Research Authority
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intension To Treat
IWRS	Interactive Web Response Systems

LEfSe	Linear discriminant analysis effect size
LFT	Liver function tests
LTFU	Lost To Follow Up
MHRA	Medicine and Healthcare Products Regulatory Agency
MSCs	Mesenchymal Stem-like Cells
NGS	Next Generation Sequencing
NHS	National Health Service
NICE	The National Institute for Health Care Excellence
QP	Qualified Person
PI	Principal Investigator
PIS	Participant Information Sheet
PSF	Pharmacy Site File
PPI	Patient and Public Involvement
R&D	Research and Development
RCOG	The Royal College of Obstetricians and Gynaecologists
RCT	Randomised Controlled Trial
RM	Recurrent Miscarriage
SAE	Serious Adverse Event
sd	Standard Deviation
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
STAMP	Statistical Analysis of Taxonomic and Functional Profiles
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
UHCW	University Hospitals Coventry and Warwickshire NHS trust
uNK	uterine Natural Killer
WCTU	Warwick Clinical Trials Unit

1. INTRODUCTION

The purpose of this trial is to find out if a short course of antibiotics will treat chronic endometritis and reduce miscarriage in women who have experienced two or more consecutive miscarriages. Endometritis is an inflammation of the endometrium (lining of the womb). The group of microorganisms that live in our bodies is called the microbiome and if there is an imbalance of the microbiome (dysbiosis) in the reproductive tract this may cause inflammation of the endometrium. The endometrium is important for implantation of the ovum (egg and sperm) and to support the fetus as it develops. Endometritis may disrupt implantation and lead to miscarriage. Endometritis has been linked to miscarriage and it is suggested that reducing the inflammation, with a course of antibiotics, will reduce miscarriages.

1.1 Background

1.1.1 Epidemiology and burden of the condition

Recurrent miscarriage (RM) causes considerable distress and psychological morbidity for women and their partners. The vast-majority of couples receive supportive care only, as few treatments have been shown to prevent miscarriage. The patient-led James Lind Alliance priority setting partnership has identified '*effective interventions to prevent miscarriage*' as a number one research priority.[1]

1.1.2 Chronic Endometritis and Recurrent Miscarriage

A healthy endometrium is important for successful implantation and support of the developing fetus. The bacteria that colonise the endometrium and vagina, known as the microbiome, play an important role in the endometrial health. Dysbiosis, an imbalance of the microbiome may cause inflammation of the endometrium, known as Chronic Endometritis (CE) and lead to miscarriage. Antibiotics can reduce this inflammation; although this treatment is available at private clinics and in some European countries, there is no robust evidence to support this approach and the effect of antibiotics on the microbiome is unclear.

1.1.3 Diagnosing Chronic Endometritis

Initially, the diagnosis of chronic endometritis was based on Haematoxylin and Eosin (H&E) staining of tissue sections,[2] but the identification of plasma cells on morphology alone is cumbersome and associated with substantial significant inter-observer variation. During differentiation, plasma cells acquire expression of CD138 (syndecan-1). Immunohistochemistry (IHC) with antibodies to CD138 reliably identify plasma cells[3] with increased sensitivity,[4] increased concordance between pathologists,[5] and reduced inter- or intra-observer variability when compared to H&E staining.[6] Thus, IHC is now the method of choice for identification of plasma cells. Plasma cells are not normally present in high numbers in normal endometrium.

1.1.4 Chronic Endometritis and the Microbiome

CE is thought to be caused by the presence of an array of microorganisms and a lack of lactobacilli in the endometrium, an imbalance termed dysbiosis.[7-11] Three separate studies reported that a two-week course of the antibiotic doxycycline 'cured' CE in over 90% of cases.[9]

[12-14] Additionally, non-randomised, observational studies suggest that treating CE with doxycycline prevents miscarriage.[9 12 15 16]

1.1.5 Evidence that CE is a treatable cause of miscarriage

Our systematic review did not identify any RCTs of the use of antibiotics for the treatment of CE or for the prevention of miscarriage. Meta-synthesis of non-randomised studies of women with reproductive failure, from any cause, revealed that the prevalence of CE varies between 9%-57%; reflecting the different methods and criteria used for diagnosis. Our analysis of live births in non-randomised cohort studies in women who conceived following a diagnosis of CE indicated that:

1. The live births versus miscarriages in treated versus untreated CE could not adequately be assessed as the studies were too small to reliably identify important differences.[15 16]
2. The live birth following treatment of CE was similar to that of patients without CE. These data imply that treating CE improves the live birth rate to that of women with no CE. However, these studies were small, single centre, non-randomised and used varying treatment regimens.
3. There are more live births in women treated for CE which resolved than in those in whom the CE persisted after treatment again suggesting a positive effect of treatment but in observational studies only.

1.1.6 Evidence of endometrial microbiome dysbiosis in CE

Although the pathophysiology of CE is poorly understood, the presence of plasma cells is thought to reflect either chronic infection or chronic inflammation.[2] It has been suggested that the presence of plasma cells reflects an immune response to pathogens within the uterine cavity that ascended from the lower genital tract.[17] Several studies have sought to identify and characterise these microorganisms; however, recent application of culture-independent sequencing approaches demonstrated that the endometrium is not a sterile environment, as previously believed.[18] Instead the endometrium harbours its own unique microbiome.[19] This has been replicated in other tissues previously believed to be sterile, including the lung, placenta[20] and lower urinary tract.[21] As such the identification of organisms may not represent pathological colonisation but rather a healthy balance of microorganisms that are essential for the optimal function of the endometrium. Dysbiosis of the endometrial microbiome may account for plasma cell infiltration in CE. Next Generation Sequencing (NGS) of bacterial 16S ribosomal RNA genes has been undertaken to characterise the endometrial microbiome. Like the vaginal microbiome, the endometrium is typically dominated by *Lactobacillus spp*.[22 23] The endometrial microbiota of patients undergoing Assisted Reproduction Techniques (ART) was found to be similar to that of the vagina.[8 24] However, differences in the vaginal and endometrial microbiome imply they are not merely a continuation of each other, but distinct environments with a similar yet unique microbiome.[24] Compared to a normal endometrial microbiome (>90% *Lactobacillus* spp), *Lactobacillus spp.* depletion (<90%) is associated with significantly poorer ART outcomes implantation,60%v33%p=0.03, on-going pregnancy, 59% v13% p=0.02 and live birth rates, 58% v 7% p=0.002).[24]

A comparison of the microbial profile in recurrent implantation failure patients demonstrated that those with CE had a higher detection rate of specific species, including *Corynebacterium*

(RR, 19.60*) and Mycoplasma hominis* (RR,5.04), compared to those without CE.[9 25] Another trial focussing on endometrial polyps reported that the endometrial microbiome was more diverse in CE confirmed by IHC.[8] Further, using the less sensitive culture techniques, organisms were detected in 73% of CE cases,[7] *Ureplasma uraelyticum* in 10% and *Chlamydia trachomatis* was 2.7%.[7] Using sequencing techniques the presence of these organisms detected by culture was associated with a reduction in *Lactobacillus* spp*.,* indicative of dysbiosis[10] and poor pregnancy outcomes.[11]

1.1.7 Evidence of the impact of CE on endometrial function

Our literature search identified no studies on how CE impacts on endometrial function. RM is associated with inadequate preparation of the endometrium for pregnancy, a process termed decidualisation.[26] Because of menstruation, decidualisation is a reiterative process, linked to cyclic activation of mesenchymal stem-like cells (MSCs) and their subsequent differentiation into mature stromal cells in regenerating endometrium.[26 27] Clinically, endometrial MSC deficiency,[27] heightened cellular senescence, prolonged inflammation[26 28] and impaired decidualisation potential of endometrial stromal cells[29] are strongly linked to RM, but whether or not these defects are caused by CE is not known.

1.1.8 Evidence of efficacy of doxycycline treatment

The most frequently used antibiotic regime in published studies is doxycycline (100mg twice daily for 14 days). Based on analysis of repeat endometrial biopsies, a single course of doxycycline was reported to 'cure' histologically defined CE in 92%,[9] 94%[12] 75%,[13] and 70%[14] of patients. Following doxycycline treatment, changes to the endometrial microbiome have been identified. Notably, the detection rates of Corynebacterium, Enterococcus, Escherichia coli, Streptococcus agalactiae, Ureaplasma urealyticum and Ureaplasma parvum were significantly lower following antibiotic treatment.[9] This reduction in pathogenic microorganisms was associated both with a significant increase in Lactobacillus spp, the major resident species within the uterine cavity[30] and a reduction in the number of plasma cells within the endometrial stromal compartment.[9] This suggests a shift towards a normal microbiota following doxycycline treatment. Importantly, no trial to date reported on the persistence of CE on repeat biopsies in non-treated women. We found that ≥12 CD138+ cells/mm2 persisted in only 78% of untreated women when biopsied again after two or more cycles (n=32).

These observations suggest that CE may resolve spontaneously, or be intermittent, in some women but persists in others. Further, in addition, to its antibacterial properties, doxycycline has a well-documented anti-inflammatory effect,[31] raising the possibility that it is useful for the treatment of CE not associated with endometrial symbiosis.

1.2 Proposed trial

A prospective, multi-centre, randomised, double blind adaptive designed trial, comparing a pre-conception 14 day course of doxycycline to placebo in up to 1500 women with recurrent miscarriage associated with chronic endometritis.

1.3 Target population

Women aged between ≥18 to <42 at registration who have experienced two or more consecutive first trimester miscarriages.

1.4 Chronic Endometritis Diagnosis

Chronic Endometritis will be diagnosed based on the density of CD138 staining cells within a tissue section of the biopsy. A positive screen will be defined as ≥5 CD138 positive cells per $10mm^2$.

1.5 Treatment

Women who screen positive for CE, are eligible and wish to participate will be randomised to either doxycycline 100 mg or matching-placebo twice a day for 14 days.

2. RATIONALE

2.1 Aims and hypothesis

The aim in this trial is to determine if doxycycline administered prior to conception improves pregnancy outcome in women with recurrent miscarriage associated with chronic endometritis and explore the mechanisms by which it could prevent miscarriage.

2.2 Justification

There is increasing evidence in the literature that CE is a treatable cause of RM. CE is persistent inflammation of the endometrium, detected by the presence of plasma cells in the endometrium and linked to miscarriage. The incidence and nature of endometrial dysbiosis associated with CE in RM has not been studied systematically; nor is it known if CE in RM is associated with sterile inflammation or chronic dysbiosis. It is not known if CE causes or compounds the endometrial defects associated with RM. It is also not known if resolution of CE, in response to doxycycline treatment, reverses endometrial defects.[27 32 33] Observational studies suggest that antibiotic treatment may be effective in preventing miscarriage in women with CE, but this has not been tested in a randomised double-bind placebo controlled trial. Our observations suggest that CE may resolve spontaneously in some women but persists in others. Hence, there is a genuine need for placebo-controlled trial to determine the efficacy of doxycycline treatment on the subsequent on-going pregnancies in women with recurrent miscarriage associated with chronic endometritis.

2.3 Assessment and management of risk

A risk assessment has been completed by the Sponsor. The risk assessment will cover all risks associated with the trial and trial management. It will be updated on a continual basis as the risks change throughout the life of the trial.

2.3.1 Risk of Pregnancy

In the summary of product characteristics (SPC) doxycycline is contra-indicated in pregnancy, because tetracycline use has been associated with problems with infant's teeth and bone development. However, a meta-analysis by Cross and colleagues (2016)[34] reported an absence of evidence of harmful effects when taken in pregnancy and there are no known reported cases or evidence of harm from taking doxycycline from day 1 to 14 of the menstrual cycle. Doxycycline is prescribed to pregnant women "*when travel to malarious areas is unavoidable during pregnancy, doxycycline can be used for malaria prophylaxis if other regimes are unsuitable, and if the entire course of doxycycline can be completed before 15 weeks' gestation*" (BNF, 2018-2019). This trial has been designed so there is minimal chance of fetal exposure in the following ways:

1. A pregnancy test is performed prior to taking doxycycline
2. Doxycycline/placebo is taken on the first day of the menstrual cycle so women are not pregnant when they start taking the intervention
3. The doxycycline/placebo are taken prior to ovulation, hence before pregnancy is possible – we review all women's cycles
4. Women are advised and consent to use condoms
5. The half-life of doxycycline is 16-22 hours thus there will be minimal drug present one week after the drug is stopped should implantation occur.[10]

The doxycycline/placebo will start on the first day of their next menstrual cycle. We plan to start the intervention on day one of the cycle to ensure that the treatment is completed during the proliferative phase of the cycle, thus negating the risk of doxycycline exposure in early pregnancy.

If a participant reports she is pregnant during the month they are taking the doxycycline/placebo, they will discontinue taking the doxycycline/placebo and will be reassured that the risk to her infant is extremely small.

3. OBJECTIVES AND OUTCOME MEASURES

3.1 Primary objective

Does doxycycline given prior to conception improve the number of on-going pregnancies and total live births in women with recurrent miscarriage associated with chronic endometritis?

3.1.1 Primary outcome measures

This trial will use an adaptive design methodology so that we can stop the trial early in the case of better than expected efficacy or futility. Therefore we need two primary outcome measures. One that is reached earlier than the whole 40 weeks of pregnancy. Hence, one explanatory, primary outcome measure will be ongoing pregnancy.

3.1.2 Primary Outcome 1

The first explanatory primary outcome measure will be on-going pregnancy at 12 weeks. Ongoing pregnancy is defined as the number of viable pregnancies, with a crown rump length >54 mm, reaching 12+6 weeks of gestation as a percentage of the total number of first pregnancies after the intervention. As 98% of miscarriages occur before 12 weeks, the number of ongoing pregnancies will be very similar to number of live births.

3.1.3 Primary Outcome 2

The second pragmatic primary outcome measure will be the total live births defined as total live births plus ongoing pregnancies at the end of trial. Defined as: On-going pregnancy at 12+6 weeks gestation

$$\frac{\text{the presence of a fetal heart beat when the Crown Rump Length >54mm}}{\text{total number of women randomised}}$$

- Total live births = Projected live births >24 weeks in first or subsequent pregnancy analysed at the end of the trial as proportion of women (whilst some babies born at 22 and 23 of weeks of gestation survive, they are at risk of long term disability and hence will not be included in this outcome measure).
- The maximum denominator for both of these analyses will be the 1,500 women randomised. This change does not affect any of our simulations for likelihood of early stopping.

3.2 Secondary objectives

1. To find out if doxycycline treatment improves CE?

2. To examine the separate effects of doxycycline on conception, early miscarriage, and late miscarriage. In addition, assess the mediation effect of each of these, on the primary outcome, with treatment effect as a covariate.

3.2.1 Secondary Outcome measures:

- Density of CD138+ cells in the endometrium before and after treatment

- Time to first conception
- Anticipated time to first live birth
- Live births, the proportion of women with a live birth after 24 weeks of gestation in their first pregnancy after randomisation.
- Pregnancy complications, in first pregnancy following randomisation lasting greater than 12 weeks; second trimester miscarriage, intrauterine death, preterm delivery, small for gestational age and placental abruption..
- Early pregnancy complications (e.g. ectopic pregnancy, molar pregnancy).
- Type of miscarriage, biochemical[1], gestational sac[2], fetal[3], karyotype of miscarried tissue.
- A re-assessment of the ability of the CD138+ cell test to detect which patients will benefit from Doxycycline will be undertaken. This analysis will use on-going pregnancy and live births per patient in women excluded from randomisation by having low CD138+ cell scores and those randomised to placebo.
- Termination for social reasons

[1] *Biochemical – Positive pregnancy test without ultrasound visualisation of pregnancy*

[2] *Gestational Sac – Presence of gestational sac on ultrasound without visualisation of fetus*

[3]*Fetal – Presence of fetus on ultrasound with no fetal heart beating*

3.3 Exploratory Objectives

1. To find out if doxycycline treatment changes Lactobacillus-deplete microbiota to a Lactobacillus-dominated microbiota?

2. To find out if doxycycline treatment, improves the differentiation potential and colony-forming activity of endometrial stromal cells?

3. To find out if CE is related to heightened senescence of endometrial stromal cells?

3.3.1 Exploratory Outcome measures

1. Evaluate change of Lactobacillus-deplete microbiota to a Lactobacillus-dominated microbiota after treatment.

2. Assess changes in differentiation potential and colony-forming activity of endometrial stromal cells after treatment.

3. Assess senescence associated β Galactosidase activity in patients with CE.

4. TRIAL DESIGN

This trial is a prospective, multi-centre, randomised, double blind adaptive designed trial, comparing a pre-conception course of doxycycline against placebo in up to 1500 women from sites in the United Kingdom. The trial is an adaptive design that allows frequent statistical review; leading to either continuation, stopping or adapting the trial to ensure maximal efficacy. Adaptive trial designs have the potential to markedly reduce the overall cost and duration of the trial by using interim statistical analysis, and modifying the design in the light of information already accumulated (e.g. stopping early or extending recruitment). Using on-going pregnancy as a surrogate marker for live birth markedly reduces the overall cost and duration of the trial by reducing the time to knowledge of the outcome and builds in the necessary flexibility to enable an adaptive trial design. Our pragmatic primary outcome measure that is more meaningful to patients will be total live births, both actual, or anticipated, first live births, at the end of trial data collection including all completed, or ongoing, second or subsequent pregnancies after randomisation. The live birth outcome will include the effects doxycycline treatment may have on fertility, preterm birth, second trimester miscarriage and stillbirth.

We anticipate that around 3,062 women will have an endometrial biopsy, during the luteal phase of the women's menstrual cycle, to test for CE, defined as ≥5 CD138 positive cells per $10mm^2$. It is estimated that 50% will screen positive and be invited to participate in the randomised trial. Ongoing pregnancy at 12+6 weeks of gestation in the first pregnancy after randomisation is our primary explanatory outcome measure. Since 98% of all miscarriages occur prior to 12 weeks of pregnancy, ongoing pregnancy is a very good early marker of live births.[35]

The trial comprises two stages:

1. Patients will be registered into the screening trial and have an endometrial biopsy taken to test for the presence of CE (N=3,062)
2. Women who screen positive for CE will be randomised into the randomised controlled trial of doxycycline versus placebo (N=1,500).

Within the main trial (CERM A) a subset of patients will be recruited to CERM B to determine if doxycycline treatment improves CE and microbiota compositions.

CERM B patients will all be recruited at University Hospital Coventry and Warwickshire NHS Trust. CERM B patients will follow the same pathway as CERM A patients but will have the following additional assessments:

- Patients will be registered into the screening trial, consented to the CERM B trial and have a vaginal, endometrial and cervical swab at registration.
- Women who screen positive for CE and are randomised into the trial will have a second endometrial biopsy following treatment.
- Women who screen positive for CE and are randomised into the trial will have a second vaginal, endometrial and cervical swab following treatment.

In order to analyse if doxycycline treatment improves CE and microbiota composition 200 paired endometrial biopsy and endometrial swab samples are required from patients before and after treatment. Approximately 400 patients will be registered into CERM B and have the additional vaginal, endometrial and cervical swab at registration. Approximately 200 of these patients will screen positive for CE and be randomised into the trial. These patients will have the repeated endometrial biopsy and vaginal, endometrial and cervical swab following treatment. A random sample of vaginal and cervical swabs will be analysed to ensure no contamination of the endometrial swab sample.

5. TRIAL SETTING

Women will be recruited from NHS Recurrent Miscarriage Clinics (RMC), Early Pregnancy Units (EPU) or through Tommy's 'Recurrent Miscarriage' database in 10 NHS organisations across the UK.

5.1 Site requirements:

- Sites must be able to take endometrial biopsy samples. Sites must adhere to the CERM A Manual for collection of Endometrial Biopsies for the collection, shipment and tracking of endometrial biopsy samples.
- Sites must follow pharmacy procedures detailed in the trial treatments section of the protocol , including IMP labelling, storage, dispensing and accountability procedures.
- Sites must adhere to the data collection requirements given in the data management section of the protocol.
- Sites must comply with the CERM Trial monitoring procedures set out in the monitoring, audit & inspection section of the protocol.

All NHS organisations taking part in the trial will be responsible for registering and randomising patients into the CERM Trial.

University Hospitals Coventry & Warwickshire NHS Trust will also be responsible for recruiting CERM B patients.

5.2 Site Initiation

Before the trial can be initiated at site, the prerequisites for conducting the trial must be clarified and the organisational preparations made with the trial site. The trial manager will arrange a site initiation visit which must be attended by key trial personnel at the site including the PI and pharmacy lead. This visit involves a detailed presentation of the trial documents and discussion of unanswered questions. The PI is responsible for ensuring that all of the information presented at site initiation is passed on continuously to all those who are involved in the conduct of the trial

Following site initiation, the research team will be in regular contact with sites by email, telephone and face-to-face, to support with the day-to-day management of the trial, and identify and discuss any problems with compliance to the protocol, recruitment pathway, barriers to recruitment, 'Site File' completeness.

5.3 Site staff Training

5.3.1 Principle Investigator (PI)

An appropriate, medically qualified, PI should be identified at each NHS organisation. The PI will have overall responsibility for the conduct of the trial at site. The PI will be responsible for:

- Ensuring that the trial is conducted as set out in the protocol and supporting document

- Delegating trial related responsibilities only to suitably trained and qualified personnel and ensuring that those with delegated responsibilities fully understand and agree to the duties being delegated to them
- Ensuring that CVs and evidence of appropriate training for all Site staff are available in the Trial Site File
- Ensuring that all delegated duties are captured in the trial Delegation Log
- Ensuring all Adverse Events are documented and reported appropriately to the WCTU CERM trial team.
- Accountability for trial treatments at their site.
- Ensuring the trial is conducted in accordance with ICH GCP principles
- Allowing access to source data for monitoring, audit and inspection
- Ensuring that all source data is complete and provided to the WCTU CERM trial team at regular intervals.

5.3.2 Research Team at site

All staff involved in trial specific duties will be required to have completed a Good Clinical Practice course and keep their knowledge up-to-date throughout the life-time of the trial.

5.3.3 Clinicians confirming eligibility

Clinicians confirming patient eligibility must be medically qualified.

5.3.4 Clinicians performing endometrial biopsies and vaginal, endometrial and cervical swabs

Clinicians taking biopsies and swabs will be competent to do so either by virtue of clinical role or appropriate specialist training on the technique for the trial (provided by CI or delegate). Trial specific guidance will be provided in the CERM A Manual for collection of Endometrial Biopsies and CERM B Manual for collection of Microbial Swabs. Clinicians taking biopsies and swabs are not required to have GCP training or be on the site delegation log if this procedure is routine in their clinical role.

6. ELIGIBILITY CRITERIA

As per GCP the decision as to whether a patient is eligible for entry into the trial is considered a medical decision and therefore this decision must be made by a medically qualified doctor.

Appropriately qualified staff assigned this responsibility must be named on the trial delegation log.

Confirmation of eligibility must be documented in the patients' medical notes.

WCTU CERM trial team will be available to answer any queries regarding eligibility criteria prior to registering a patient into the trial.

6.1 Inclusion criteria - screening

- Age ≥18 to <42
- Two or more consecutive first trimester miscarriages
- Women who agree to use barrier methods of contraception during the following cycles: biopsy preparation, screening-biopsy, waiting for the results and during the intervention.

6.2 Exclusion criteria – screening

- Treatable cause(s) of RM for example:
    - antiphospholipid antibody syndrome
    - thyroid disease
    - parental karyotypical abnormalities.
- Known sub-septate uterus.
- Poorly controlled diabetes (HbA1c >48mmol/mol)
- Allergy to doxycycline or its excipients.
- Doxycycline contraindicated
- Antibiotics in the current menstrual cycle
- Taking a medication that may interact with doxycycline – refer to table 8 for a full list.
- Myasthenia Gravis.
- Systemic lupus erythematosus (SLE).
- Immunodeficiency disorder.
- Alcohol dependency*
- Long-term antibiotic(s) use.
- Menstrual cycle ≤21 - ≥42 days.
- Unable to give informed consent.
- Participation in another clinical trial of an investigational medicinal product (CTIMP) in the last 90 days.
- Women who are breast feeding.
- Pregnancy

6.3 Inclusion criteria - RCT

- Women with ≥5 CD138+ cells/10mm^2.

6.4 Exclusion criteria – RCT

- A course of antibiotics between screening registration and randomisation to RCT**
- A delay of longer than three months between biopsy result and randomisation to RCT**
- Known serious liver disease*[1]
- Taking a medication that may interact with doxycycline – refer to table 8 for a list of known interactions.
- Any co-morbid disease or condition that would make the patient unsuitable for the trial*[1]
- Pregnancy

* As judged by a medically qualified doctor assessing trial eligibility informed by referral letter from GP and hospital records

**If a woman has a course of antibiotics between screening registration and randomisation or was registered for screening over three months before randomisation to the RCT they will not be eligible for trial randomisation at the time. These women should be given the option to re-screen and have another biopsy to confirm eligibility for randomisation.

[1] If a clinician has doubts about a participants' suitability for the trial because of a long-term medical condition they should undertake a Full Blood Count (FBC) and Liver function tests (LFTs); in order for a woman to be included in the trial the following should apply:

- WBC >$3x10^9$/L,
- Neutrophils >$1.5x10^9$/L,
- Platelets >$75x10^9$/L, Hb>100g/L
- Bilirubin <1.5XULN*
- AST/ALT <3xULN*
- Albumin >30g/dL).

* ULN = Upper Limit of Normal
All required additional checks must be documented in the patients' medical notes

6.5 CERM B Exclusion (repeat endometrial biopsy and vaginal, cervical and endometrial swabs)

- Pregnancy

7. TRIAL PROCEDURE

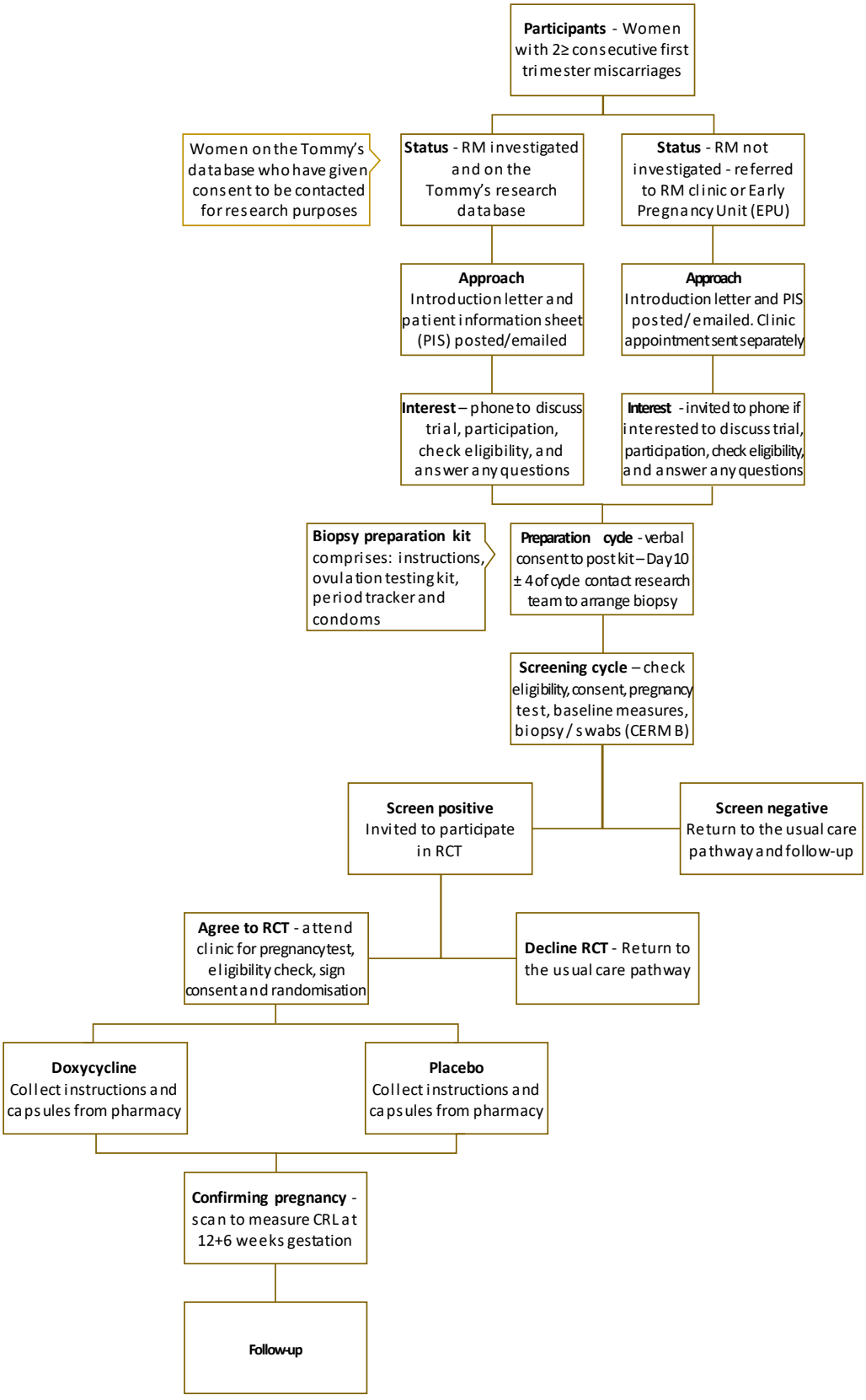

Figure 2 – Pathways to recruitment

7.1 Patient Identification

Women will be identified to participate in one of the following two ways:

7.1.1 Women on the Tommy's 'Recurrent Miscarriage' database

Women on the Tommy's 'Recurrent Miscarriage' database have had investigations for a treatable cause of their miscarriage and have given consent to be contacted for research purposes. These women will be sent an introduction letter and a screening participant information sheet explaining about the trial and what participation would involve, either by post or email depending on their stated preference. After one week women will be contacted, by telephone, by a member of the hospital research team to discuss the trial, answer any questions and discuss participation.

7.1.2 Women referred to a recurrent miscarriage clinic

Women with a clinician referral to a recurrent miscarriage clinic from a gynaecologist, obstetrician, EPU or General Practitioner (GP) who have not had investigations into the cause of their RM will be sent an appointment to attend for investigations as per standard practice by the direct care team.

Separately a member of the hospital research team will send women an introduction letter and a screening participant information sheet explaining about the trial and what participation would involve and inviting women to contact a member of the hospital research team if they would like more information or to participate in the trial.

If a treatable cause of their recurrent miscarriages is identified they will receive treatment and will not be eligible for the trial. If a treatable cause of their recurrent miscarriages is not identified they will be eligible for the trial.

If women on either pathway would prefer to talk about the trial and what participation would mean for them face-to-face this will be arranged.

Women who self-refer will be advised to contact their GP to discuss referral to one of the recurrent miscarriage clinics taking part in the trial.

7.1.3 Screening Log

A Screening Log must be maintained by each site to document all patients considered for the trial even if subsequently not entered into the trial. Where possible, the reason for non-entry to the trial must be documented. This must be faxed or emailed to WCTU CERM trial team on a regular basis when requested. Patient names or hospital numbers must not be recorded on the Screening Log.

7.2 Pre-Screening

It is important to women, who are trying to conceive, to minimise the time they are using contraception, therefore to reduce this time we are asking women to prepare for their biopsy before they attend clinic. If women on either pathway would like to participate, their initial eligibility will be checked and verbal consent will be taken and documented in their medical notes. Confirmation of verbal consent should also be recorded on the CERM trial screening

log. A biopsy preparation kit which includes a period tracker, condoms and a ovulation testing kit will be posted out or given to women if they meet face-to-face with a member of the hospital research team. Instructions on using the kit will be included. Women will contact the clinic when they are ovulating or if the test does not indicate ovulation on day 23, to arrange to come into clinic for a biopsy.

7.3 Screening

To enter the trial women will be asked to consent to use contraception for either two or four menstrual cycles depending on whether they screen positive for CE (Table 7). However, this may be longer if a women does not use contraception, has a condom failure during one of the cycles or personal circumstances intervene.

Table 7 – trial cycles

Cycle	Procedure
1	Biopsy preparation
2	Screening: endometrial biopsy, microbial swab of the vagina*, endometrium* and cervix* and if there is an indication of liver failure a blood test may be taken
3	Results of screening
4	RCT for screen positive women

*CERM B only

The endometrial biopsy will be taken in the luteal phase of the cycle at around (10 ± 4) days after ovulation. Instructions in the 'biopsy preparation kit' will request women to record their menstrual cycle, starting from the first day of bleeding in their next period, using the period tracker provided. The instructions will emphasise the importance of using condoms and not having unprotected sexual intercourse. Condoms are provided and more can be obtained by contacting the hospital research team, family planning services and some GP surgeries.

7.3.1 Consent for screening

When the woman comes to clinic for their biopsy they will meet with a member of the hospital research team who will explain the process and answer any questions. Women will be informed that they are welcome to bring a partner, family member or friend to this meeting. Eligibility for the trial will be checked by a medically qualified doctor. A pregnancy test will be undertaken, if the test indicates the women is pregnant, the biopsy will not be taken and she will be referred to her GP who will arrange her care. Women will confirm participation in the trial by signing a screening consent form. The consent process will be documented in the participants medical notes.

Following consent the site research team should ensure that patients have been given a copy of the signed screening informed consent form and screening PIS.

7.3.2 Consent CERM B

Women attending UHCW RM clinic will be asked to consent to CERM B. These patients consent to having a microbial swab of the vagina, endometrium and cervix taken in addition

to the endometrial biopsy. These patients will be given the option of consenting to CERM A if they do not wish to have the microbial swabs.

Following consent the site research team should ensure that patients have been given a copy of the signed CERM B screening informed consent form and CERM B screening PIS.

7.4 Registration – screening

The site should log on to the CERM registration/randomisation portal to register the participant and obtain a trial ID number to identify the participant for the purposes of the trial. Sites should access the portal via the link below:

http://ctu.warwick.ac.uk/CERM

Site staff authorised to register and randomise participants to the CERM trial will be provided with a username and password to access the registration and randomisation system as part of the site set up process.

In the unlikely event the registration/randomisation portal is not available please contact the WCTU CERM Trial Team (contact details given in Table 4) who will be available week days between 09:00 and 17:00 (16:00 on Fridays).

An email will be sent to the PI and lead contact at site confirming patient registration details and trial ID number.

Following registration the site research team should ensure that they update the patient screening log and ensure the participants details are entered on to the local sites participant enrolment log.

Refer to the tissue sample section of the protocol for details on the collection and shipment of the endometrial biopsy and microbial swab of the vagina, endometrium and cervix.

7.5 Biopsy results

Results of the biopsy will be received up to four weeks after receipt of biopsy by the central laboratory (UHCW).

Once results have been received the investigator should complete and send participant's General Practitioner (GP) a letter and copy of the Participant Information Sheet for screening to inform them of their patient's participation in the trial. If women who screen positive for CE are subsequently randomised, the investigator should also send a copy of the Participant Information Sheet for the RCT with the GP letter. The CERM B PIS for screening and RCT should be sent as appropriate.

7.6 Randomisation

It is expected that half the women will screen positive for CE. If the results indicate that a women has CE she will be invited to participate in the randomised controlled part of the trial to receive either a course of doxycycline an antibiotic (the intervention group) or placebo (the control group).

7.6.1 Consent to participate in the RCT

Women who screen positive for CE will be contacted to inform them of their results and to discuss participation in the RCT. An appointment will be made to meet with a member of the hospital research team who will explain the RCT and what participation would involve including the potential risks and benefits of participating. If women would like to receive more information regarding the RCT before the appointment then an RCT PIS can be posted or emailed to them. All women will have as much time as they need to consider participating in the RCT, have the opportunity to discuss participation, ask questions and consult with health care professionals, family and friends.

Eligibility will be checked and the women will confirm participation in the RCT by signing the RCT consent form. Consent must be taken by a medically qualified doctor. A pregnancy test will be undertaken, if the test indicates the women is pregnant, she will be referred to her GP who will arrange her care. If the pregnancy tests indicates the woman is not pregnant she will be randomised to receive doxycycline/placebo. The consent process will be documented in the participants medical notes.

Following consent the site research team should ensure that participants have been given a copy of the signed RCT consent form and PIS.

7.6.2 Consent to participate in the RCT CERM B

Women attending the UHCW site will be asked to consent to the CERM B RCT. These participants will consent to having a second endometrial biopsy and vaginal, endometrial and cervical swabs being taken.

Following consent the site research team should ensure that participants have been given a copy of the signed CERM B RCT informed consent form and PIS.

Screen-positive women in CERM B will have a biopsy during the luteal phase (10 ± 4 days) after ovulation during the intervention cycle. CERM B participants should be provided with a second biopsy preparation kit. The preparation, procedure and analysis will be identical to the first biopsy procedure (see the tissue samples section of the protocol for further details).

7.7 Randomisation – Randomised Controlled Trial

The trial ID number allocated during registration will be used as part of the randomisation process.

Sites should log on to the CERM registration/randomisation portal to randomise the participant and obtain a drug pack number. Sites should access the portal via the link below:

https://ctu.warwick.ac.uk/CERM

In the unlikely event the registration/randomisation portal is not available please contact the WCTU CERM Trial Team (contact details given in table 4) who will be available week days between 09:00 and 17:00 (16:00 on Fridays).

Women will be randomised using minimisation, balancing age and number of previous miscarriages, as these are the two most important predictors of pregnancy outcome in women with RM.

An email will be sent to the PI and lead contact at site confirming participant randomisation details, trial ID number and participant drug pack number.

Following randomisation the site research team should ensure that the participant's details are updated onto the local site's participant enrolment Log.

Once a participant is randomised they should be provided with the 'Taking my capsules on the CERM trial: Chronic Endometritis and Recurrent Miscarriage' leaflet and instructed as follows:

- Take one capsule, twice a day, 12 hours apart for 14 days starting on day one of their menstrual cycle.
- Use condoms and to not have unprotected sexual intercourse during their entire menstrual cycle and not just whilst taking the doxycycline/placebo. This is the last cycle women will be asked to use condoms and to not have unprotected sexual intercourse.
- Given a CERM Trial participant card. This should be carried with the participant at all times. If a replacement is needed they should contact their local site research team.
- Participants should be reminded to undergo a urine pregnancy test as soon as their menstrual periods are delayed or a pregnancy is suspected and to contact the site research team immediately.

7.8 Blinding

The trial is a double blind trial the participants, clinicians, pharmacist or the research team do not know the treatment allocation. All drug packs containing either doxycycline or placebo will have an individual pack number but are otherwise identical. Unblinding is possible if clinically necessary (figure 3).

7.8.1 Emergency unblinding

A request on the grounds of safety can be made by any clinician involved in the medical care of the women. The CI or delegate will consider the request and if necessary unbinding will be undertaken using the interactive voice response system linked to the Warwick CTU database. Only authorised personnel will be able to access this system using a unique user specific passcode. In the event of a suspected allergic reaction, the doxycycline/placebo will be discontinued and unblinding will be undertaken if necessary.

The unblinding will be documented on the trial database, a unblinding form will be completed with the justification and reported to the statistician, TMG, TSC and DMC. If an emergency unbinding request is not actioned a unblinding form will be completed with the justification and reported to the statistician, TMG, TSC and DMC.

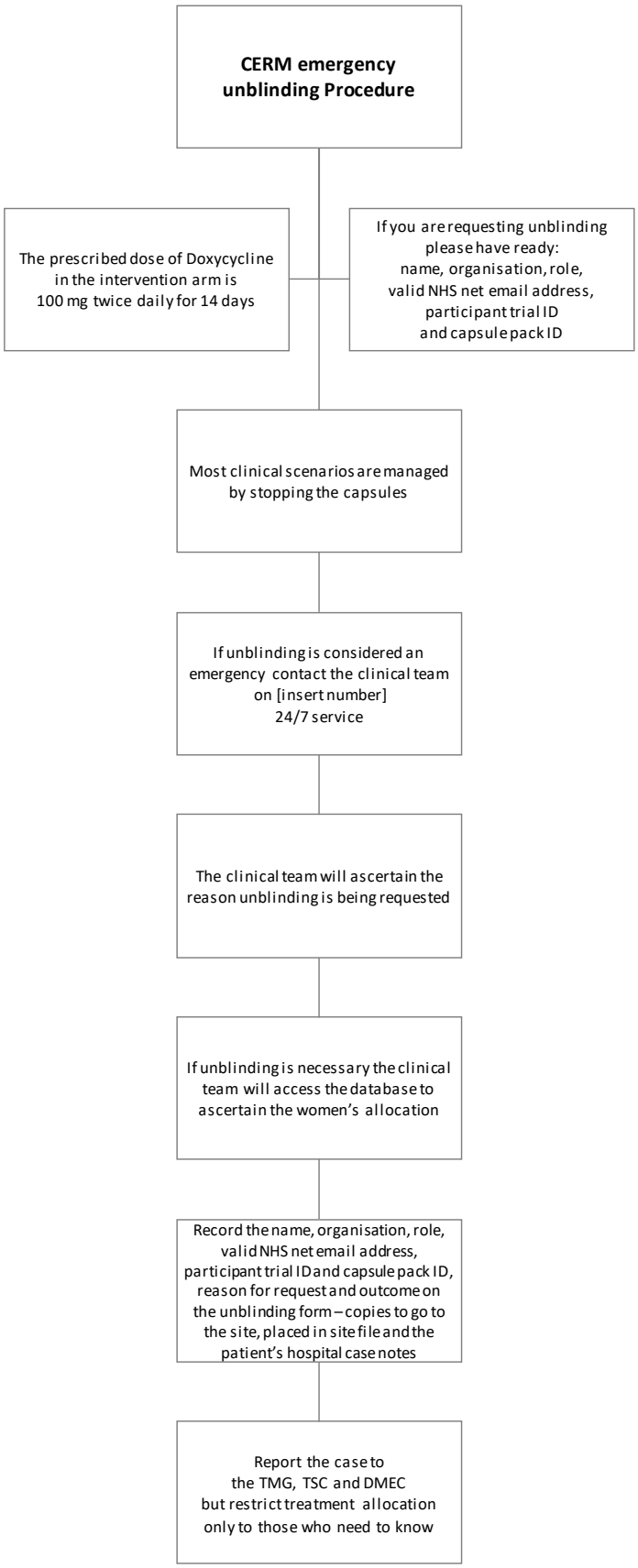

Figure 3 – Emergency Unblinding procedure

7.9 Follow up for women who screen negative for CE

If the results indicate that a woman does not have CE she will not be eligible to participate in the RCT. Women will be contacted to inform them of the results. Women will then be followed-up every 3 months to collect details of any confirmed first pregnancies conceived within 12 months from receiving the result of the endometrial biopsy until delivery or miscarriage. We will collect data on the gestation and pregnancy outcome only i.e. miscarriage, live birth, stillbirth.

7.10 Patient information and consent review and guidance

It is important for this trial that we include women who are not fluent in written and/or spoken English. Translators should be provided during recruitment to allow those who are not sufficiently fluent in spoken English to be adequately informed about the trial.

A web based resource will also be available containing all participant facing materials, an information sheet about the data we are collecting and why we are collecting it and links to key organisations are available from the trial website at: https://warwick.ac.uk/cerm.

7.10.1 Consent overview

- CERM A patients diagnosed with CE – CERM A Consent for Screening + CERM A Consent for Randomisation
- CERM A patients without CE – CERM A Consent for Screening
- *CERM B patients diagnosed with CE – CERM B Consent for Screening + CERM B Consent for Randomisation
- *CERM B patients without CE – CERM B Consent for Screening

*CERM B is for UHCW patients only

7.11 End of trial

The trial is an adaptive design that allows frequent statistical review; leading to either continuation, stopping or adapting the trial to ensure maximal efficacy. The trial will finish recruitment once 1500 women have been randomised, or before this dependent upon efficacy and futility. Any women who have already been registered into the trial prior to 1500 women being randomised, who receive a positive CE diagnosis after this date, will also be randomised. Follow-up information will be collected for 14 months after the last participant is randomised.

The trial will end when the database is locked following data entry from the last follow-up. The trial will be stopped prematurely if:

1. Mandated by the Ethics Committee.
2. The TSC, based on the recommendations from the DMC, decide the trial should end.
3. If recruitment falls substantially below target at six months i.e. ≤68 women randomised.
4. EME funding ceases.

The HRA Research Ethics Committee and MHRA will be notified in writing within 15 days if the trial has been concluded or terminated early.

8. TRIAL TREATMENTS

Intervention Arm: Doxycycline 100mg orally twice daily for 14 days.
Control Arm: Matching-placebo orally twice daily for 14 days.

8.1 Name and description of investigational medicinal product(s)
The investigational medicinal products (IMPs) are:

- Doxycycline 100mg capsules
- Matching placebo capsules

Both IMPs will be over-encapsulated and packaged to look identical in appearance, colour, shape and weight.

8.2 Regulatory status of the drug
IMP will be sourced, over-encapsulated and repackaged by Sharp Clinical Services Ltd under their MIA(IMP). Batch documentation will be held by Sharp Clinical Services and Qualified Person (QP). Batch Release Certificates will be sent directly to the sponsor and kept centrally.

Sharp Clinical Services will source Doxycycline from a product with a UK/EU marketing authorisation. The matching-placebo will be made by Sharp Clinical Services.

8.3 Product Characteristics
IMPs will have a simplified IMP dossier prepared by Sharp Clinical Services and a copy will be kept centrally by the sponsor.

The summary of product characteristics (SmPC) for doxycycline will be used as reference safety information (RSI) for the trial. This will be maintained in the TMF and will be updated periodically. Any use of an updated SmPC will be managed by WCTU with approval from the sponsor and authorisation from the MHRA will be obtained prior to use and dissemination to sites.

8.4 Drug storage and supply
IMPs will be supplied by Sharp Clinical Services who will over-encapsulate commercially available doxycycline and manufacture a matching placebo capsule. The manufacture will be done under an MIA(IMP) license following Good Manufacturing Practice (GMP) & Medicines for Human Use (Clinical Trials) Regulations 2004 as amended.

Sharp Clinical Services will assign a qualified person (QP) to be responsible for batch release and provide support for product complaints/queries for the duration of the trial. Details of specific arrangements will be documented in a GMP Technical Agreement with the Sponsor.

IMP will be supplied as blinded packs of doxycycline 100mg/placebo capsules, each containing a 14 day supply. Each pack will have a unique pack number.

8.4.1 Temperature monitoring and excursions

IMP must be stored at ambient temperature 15-25 degrees Celsius. Sites will be required to monitor the temperature using at least a min/max thermometer on a daily basis. Temperature logs should be kept either centrally on site or within the pharmacy site file. Where temperature logs are kept centrally a copy of the temperature log should be added to the pharmacy site file at the close of the trial.

A temperature excursion is defined as any temperature outside of 15-25°C. In the event of a temperature excursion either during storage or during delivery the site will need to quarantine affected stock and notify WCTU CERM trial team who will contact the Sponsor to make a decision about the usability of the stock based on any extended stability data or accelerated stability testing from the manufacturer or other published data.

8.4.2 Ordering

The WCTU CERM drug management system will be used for ordering, receipt and randomisation of IMP packs.

WCTU will order the initial supply of doxycycline/placebo for each site and will monitor stock levels at each site using the CERM drug management system. WCTU will set a minimum stock level for sites depending on recruitment, when stock levels reach this threshold WCTU will re-order supplies of doxycycline/placebo for site as required. If sites require additional stock or need to adjust their stock holding they should contact WCTU CERM trial team by email. The turnaround time for delivery of the IMP will be five working days.

8.4.3 Shipment

IMP will be delivered to sites by courier from Sharp Clinical Services using insulated shippers (e.g. AmbiTech). Each shipment will contain a single use electronic temperature monitoring device (e.g. USB TempTale 4). QP batch release certificates will not be sent to sites and will be held centrally by the sponsor. If sites require QP batch release certificates they should contact the WCTU CERM trial team.

8.4.4 Receipt

On receipt of IMP, please ensure that supplies are in good condition. Sites will need to acknowledge receipt of IMP to WCTU by email or fax. WCTU will then update details on the stock management system. Sites will download the data from the enclosed temperature monitoring device using the instructions included with the shipment and print off the PDF data.

The temperature monitoring data file and shipment paperwork will be kept in the pharmacy site file.

If stock is not in good condition please notify WCTU immediately and quarantine the stock. The sponsor will make a decision as to the suitability of stock and whether stock needs to be destroyed on site or returned to Sharp Clinical Services.

IMP should be kept segregated from general hospital supplies, in a secure location with restricted access.

8.4.5 Distribution

IMP must not be distributed to other sites without prior discussion with the sponsor.

8.4.6 Return

In the event IMP needs to be returned, WCTU will make arrangements with the site for a courier to collect.

8.4.7 Product recall

WCTU will notify sites in the event of a product recall. Any affected stock will be quarantined on site until a decision can be made about the usability of the stock.

8.4.8 Destruction

IMP must not be destroyed on site without prior approval from the sponsor or delegated representative. Sites will need to keep a record of destruction/disposal of IMP. Evidence of destruction or disposal will need to be sent to WCTU.

8.5 Preparation and labelling of Investigational Medicinal Product

The IMP will be labelled to ensure, protection of the participant, traceability, identification of the trial, identification of the product and to facilitate proper use of the IMP in accordance with Volume 4 of Good Manufacturing Practices, Annex 13 (Manufacture of investigational medicinal products).

Sample labels will be created by the Sponsor and will be provided to the MHRA for approval prior to manufacture.

Sites may add additional dispensing labels to the product as part of standard hospital dispensing practice. Any additional labelling should not contradict or obscure the product label. Any local labelling should be sent to WCTU for prior approval.

8.5.1 Prescribing and Dispensing

Following randomisation of a participant into the trial, WCTU will assign the participant pack number. The pack number assignment will be blinded and sent to the investigator and pharmacy by email.

The Principal Investigator on site or a medical doctor delegated by them will prescribe trial medication.

The prescription can be created as per local practice, but must have documented as a minimum the trial name, trial ID number, and pack number assignment. A copy of the prescription template must be forwarded to WCTU for review prior to site activation.

Dispensing will be done by the site hospital pharmacy. Packs will be dispensed according to the pack number assigned to the participant.

8.5.2 Accountability, Reconciliation and Destruction

The dispensing of the trial medication will be recorded in pharmacy on the Pharmacy IMP Accountability Log.

The accountability log should allow for full traceability. Accountability logs will record as a minimum the manufacturer, batch number, expiry dates and the participant's trial ID number, in order to maintain traceability of the stock issued and returned within the trial.

At the end of the trial any unused IMP will be quarantined pending Sponsor approval for destruction. Destruction of IMP should follow local waste disposal practice. All destruction of IMP must be recorded on the Pharmacy IMP Accountability Log.

Sites may use their own accountability logs provided they contain the minimum requirement from the sponsor and WCTU approval has been received prior to use.

8.6 Dosage schedules

8.6.1 Dose

All participants should take Doxycycline 100mg/placebo twice a day orally for 14 days starting on day one of participants' menstrual cycle.

8.6.2 Administration

The capsules should be swallowed whole with plenty of fluid in either the resting or standing position and well before going to bed for the night to reduce the likelihood of oesophageal irritation and ulceration.

If gastric irritation occurs, it is recommended that doxycycline/placebo capsules be given with food or milk. Absorption of doxycycline is not notably influenced by simultaneous ingestion of food or milk.

Please ensure participants are counselled according to the Taking my capsules on the CERM Trial: Chronic Endometritis and Recurrent Miscarriage participant information leaflet**.**

8.6.3 Missed doses

If a dose of doxycycline/placebo capsules is missed, the dose should not be doubled to make up for the missed dose, instead the missed dose should be taken within a window of 6 hours and then the next dose should be taken at the right time. A dose is considered missed if it has been more than 6 hours since it's scheduled time.

If vomiting occurs shortly after taking the dose then another dose can be taken within 2 hours of vomiting, otherwise take the next dose at the right time.

8.6.4 Precautions in renal failure

Participants can be dosed as normal in the event of acute renal failure.

There is no significant difference in the serum half-life of doxycycline in individuals with normal and severely impaired renal function.

Excretion of doxycycline by the kidney is about 40% every 72 hours in individuals with normal renal function. This percentage excretion may fall to a range as low as 1-5% every 72 hours in individuals with severe renal insufficiency (creatinine clearance below 10ml/min).

8.6.5 Precautions in hepatic failure

Participants who develop signs of hepatic failure during treatment should have IMP discontinued and be treated with standard medical care.

A clinical assessment will be made at the start of the trial and if the investigator feels there is a clinical need to have additional blood test monitoring then this can be done at the discretion of the clinician.

Women will be excluded if they have any symptoms or history of liver failure – if clinically indicated then a blood test can be done.

If applicable, CTCAE grade 1 toxicity (Bilirubin <1.5xULN, AST/ALT <3xULN, Albumin >30g/dL) will be acceptable for entry and ongoing participation into the trial.

8.6.6 Precautions in haematological toxicity

A clinical assessment will be made at the start of the trial and if the investigator feels there is a clinical need to have additional blood test monitoring then this can be done at the discretion of the clinician.

If applicable, full blood count (FBC) CTCAE grade 1 toxicity (WBC >$3x10^9$/L, Neutrophils >$1.5x10^9$/L, Platelets >$75x10^9$/L, Hb>100g/L) will be acceptable for entry and ongoing participation into the trial.

Participants should be monitored for signs and symptoms of anaemia and thrombocytopenia.

8.7 Dosage modifications

Dose reductions and dose delays are not permitted in the trial. Treatment will be discontinued for the following reasons:

- Hypersensitivity reaction to doxycycline/placebo or excipients.
- Infection.
- Participant is required to take any other antibiotics concomitantly with doxycycline/placebo.
- Pregnancy or breast feeding.
- Visual disturbances (including loss of vision) or benign intracranial hypertension.
- Haematological toxicity greater than CTCAE grade 1.
- Hepatic toxicity greater than CTCAE grade 1.
- Rashes including maculopapular and erythematous rashes.
- Non-compliance with medication.

8.8 Known drug reactions and interaction with other therapies

Table 8 - medications known to interact with doxycycline and prohibited from being taken during the intervention

Medication name
Warfarin
Penicillin
Antacids containing aluminium, calcium, magnesium or other drugs containing these cations; oral zinc, iron salts or bismuth preparations
Barbiturates, carbamazepine, primidone, phenytoin
Methoxyflurane(used as inhalation anaesthesia in emergency departments or prior to surgery)
Ciclosporin
Rifampicin
Ergotamine
Methysergide
Methotrexate
Kaolin
Sucralfate
Quinapril
Oral contraceptives
Retinoids (vitamin A or retinoids. Retinol, retinal, tretinoin (retinoic acid), isotretinoin, alitretinoin, etretinate, acitretin, adapalene, bexarotene, and tazarotene)
Oral typhoid vaccines
Fluorescence test
Drugs with the potential to cause hepatotoxicity should be avoided.
Avoid retinoids and vitamin A. Caution in use of creams that contain vitamin A or retinoids: retinol, retinal, tretinoin (retinoic acid), isotretinoin, alitretinoin, etretinate, acitretin, adapalene, bexarotene, and tazarotene.

8.9 Concomitant medication

Avoid alcohol and drugs with the potential to cause hepatotoxicity.

8.10 Trial restrictions

There are no specific dietary restrictions.

Participants must not use oral contraception and instead use barrier contraception or refrain from unprotected intercourse from the menstrual cycle prior to screening and for the duration of treatment.

8.11 Assessment of compliance with treatment

Participants will be asked to return any medication at the end of treatment. Any medication returned will be sent to pharmacy and recorded on the accountability log.

Participants will be required to keep a treatment diary of doses taken and document any missed doses. Treatment compliance will be reviewed within six weeks following randomisation (in-person or via telephone). At the end of the patient's participation in the trial any used IMP will be returned to pharmacy to be counted and destroyed.

9. TRIAL ASSESSMENTS

Please refer to the Table 5 CERM Schedule of Events which outlines the assessments at each trial Visit.

Details of all trial assessments should be written in the participants medical notes.

9.1 Screening and Registration

The following assessments should be completed during the screening and registration phase of the trial to evaluate patient eligibility. Written informed consent must be obtained prior to any trial specific assessments or investigations taking place.

- Demographics
- BMI (Height & Weight)
- Smoking history
- Medical History
- Obstetric History
- Pregnancy History
- Concomitant medication review
- Pregnancy Test
- Contraception review
- Period review

9.2 Screening

Following registration all participants will have the following assessments:

- Endometrial Biopsy

The endometrial biopsy should be handled as specified in the tissue sample section of the protocol.

9.2.1 CERM B (UHCW only n~400 participants)

- Vaginal Swab
- Endometrial Swab
- Cervical Swab

This should be taken at the same time as the Endometrial Biopsy.

9.3 Randomised Controlled Trial

The following assessments should be completed during the randomisation phase of the trial to evaluate patient eligibility. Written informed consent must be obtained for the

randomised controlled trial prior to any RCT trial specific assessments or investigations taking place.

- Confirmation of CE
- Concomitant medication review
- Pregnancy Test
- Contraception review
- Period review
- Adverse Events

CERM B participants should be provided with a second biopsy preparation kit. CERM B participants with a positive CE result should be reminded to contact the clinic when they are ovulating or if the test does not indicate ovulation on day 23, to arrange to come into clinic for a second biopsy.

9.4 Treatment completion

The following assessments should be completed (via telephone) within 6 weeks post randomisation and captured on the Treatment Completion Form:

- Daily dosage of drug
- Check if the participant has missed any doses
- Check if participant completed the full course of treatment
- Adverse Events
- Concomitant medication review
- Contraception review
- Pregnancy confirmation (if applicable)

Participants should be reminded to return their treatment diary and to take any unused medication back to pharmacy.

9.4.1 CERM B participant post treatment completion – UHCW ONLY

In addition to the assessments listed in section 9.4 CERM B participants (n~200) will undergo the following assessments 10 (+/- 4) days after ovulation following treatment completion:

- Pregnancy test
- Period review
- Endometrial Biopsy
- Vaginal Swab
- Endometrial Swab
- Cervical Swab

The UHCW research team will keep in regular contact with these participants.

Participants should be asked to bring in their treatment diary and any unused medication. Treatment completion assessments listed in 9.4 will be competed at this visit.

9.5 Pregnancy review

Participants should be reminded to undergo a urine pregnancy test as soon as their menstrual periods are delayed or a pregnancy is suspected and to contact the site research team immediately.

Communication with participants will then be via telephone until a urine pregnancy test is positive (as per local policy). At each contact a member of the hospital research team will check if participants are trying to conceive, their pregnancy status and pregnancy outcome.

9.5.1 Women wo do not have CE and are not randomised

Research staff at site should contact participants every 3 months via telephone, from the date of biopsy result until first pregnancy outcome or demise or until 12 months post biopsy result if the participant does not report a pregnancy in this time. Details of any confirmed first pregnancies should be recorded. Information on gestation and pregnancy outcome only i.e. miscarriage, live birth, stillbirth will be collected and recorded.

9.5.2 Women with CE who are randomised

Research staff at site should contact randomised participants every 3 months via telephone, from the treatment completion assessment date, until 6-8 weeks post pregnancy (>24 weeks gestation) or until the trial ends. Research staff should schedule in these calls with participants at each contact.

If a randomised participant confirms pregnancy they should be contacted at the following assessment time points and information should be collected and recorded as specified.

9.6 12 week assessment (+/-2 weeks) – standard practice 12 week scan*

- Pregnancy Confirmation (if not previously collected)
- Ultrasound (standard practice booking scan)
- Crown rump length
- Gestational Age
- Viable pregnancy assessment
- Congenital abnormality
- Concomitant medication review
- Pregnancy complications (if appropriate)
- Collect participant treatment diary (if not previously collected)
- Collect unused medication (if applicable/not previously collected)

9.7 20 – 24 week assessment – standard practice 20-24 week scan*

- Ultrasound
- Viable pregnancy assessment
- Gestational age
- Concomitant medication review
- Pregnancy complications (if appropriate)
- Congenital abnormality

9.8 Additional visits/scans as per standard practice*

If participant has an additional visit/ultrasound scan between 6 weeks - 20 week please record the following:

- Crown rump length (if recorded)
- Gestational Age
- Viable pregnancy assessment

9.9 End of pregnancy assessment or follow-up (6 – 8 weeks post end of pregnancy >24 weeks gestation)*

- Pregnancy outcome assessments
- Concomitant medication review
- Pregnancy complications (if appropriate)
- Postpartum Maternal and infant infections
- Maternal and infant infections 6 weeks post delivery

The end of pregnancy assessment should only be carried out for randomised participants who deliver a baby >24 weeks gestation. This will be the final follow up for the participant.

* These assessments may be conducted by telephone unless there is a clinical need for participants to be seen in hospital.

9.10 Payment

There are no payments for participation in this trial. We will reimburse hospital parking charges when women attend for their biopsy and biopsy results.

10. PHARMACOVIGILANCE

10.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative etiology that would explain the event.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information: • in the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SmPC) for

	that product, so long as it is being used within its licence. If it is being used off label an assessment of the SmPCs suitability will need to be undertaken. in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.

NB: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

10.2 Operational definitions for AEs/SAEs

We will follow WCTU's SOP on 'Safety Reporting' for all Adverse Events (AE) and Serious Adverse Events (SAE).

Exemptions from AE/SAE reporting

The following events listed in Table 9 will not be reported as AEs or SAEs (if hospitalisation is required) as they will be reported and recorded as part of trial efficacy outcomes and are common AEs/SAEs in this population. Comparative rates of these events will be monitored by the DMC:

Table 9 – Events collected via CRF exempt from AE/SAE reporting

Condition
Admission to hospital for miscarriage (<24 weeks)
Admission to hospital for stillbirth (≥24 weeks)
Admission to hospital for a molar pregnancy
Admission to hospital for an ectopic pregnancy
Fetal growth problems / admission to hospital for fetal growth problems
Admission to hospital for unstable lie
Admission to hospital for delivery
Admission to hospital for delayed delivery
Admission to hospital for threatened pre-term labour
Admission to hospital for pre-term birth
Admission to hospital for Caesarean section
Congenital abnormality or birth defect

If treatment or intervention is required following a medical complication that fulfils the criteria for a SAE i.e. is life-threatening or prolongs hospitalisation for any of the events listed in Table 9 then a SAE should be reported. For any of the events listed in Table 9 prolonged hospitalisation is defined by the following:

- ≥4 days for a pregnancy <24 weeks
- ≥7 days for a pregnancy ≥24 weeks

In addition some events that would meet a definition of a serious adverse event; for example admission to hospital due to nausea and vomiting, headaches or vaginal bleeding are relatively common in pregnancy. SAEs that **do not** require time critical reporting but should be reported as AEs on the Adverse Event Form are listed in Table 10:

Table 10 – Adverse Events exempt from SAE reporting but still recorded as AEs

Condition
Admission to hospital for nausea and vomiting
Admission to hospital for headaches
Admission to hospital for raised blood pressure
Admission to hospital for urinary tract infection
Admission to hospital for vaginal bleeding
Admission to hospital for pregnancy induced hypertension

10.3 Recording and reporting of AEs SAEs, SARs AND SUSARs

AEs and SAEs will be collected from the time of written consent for randomisation until 30 days post last trial treatment (last capsule taken). AEs and SAEs will not be collected for participants who do not have CE.

10.3.1 Recording of Adverse Events

All AEs (except those specified in table 9) that occur in either the participant, fetus or infant should be recorded on an Adverse Event Form and in the participants' medical notes.

If the AE is ongoing at the time of reporting then any change to the condition or outcome of the event should be reported on an Adverse Event Follow-up Form.

30 days after the participant has completed their treatment there is no requirement for the hospital research team to identify any new AEs. However, if the hospital research team become aware of an SAE that has occurred post 30 days since last treatment received and the Investigator considers the SAE to be related to doxycycline/placebo, then the Investigator should report the SAE.

Adverse Event data will be reviewed by the CERM TMG and by the DMC.

10.3.2 Reporting SAEs and SUSARs

All SAEs/SUSARs that occur in the woman, fetus or infant must be recorded on the Serious Adverse Event Form and emailed:**cerm@warwick.ac.uk** or faxed: **02476 150549** to the WCTU **within 24 hours** of the research staff becoming aware of the event. Once all resulting queries have been resolved, WCTU will request the original form be posted to the WCTU and a copy to be retained on site.

For each **SAE/SUSAR** the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- outcome
- severity assessment
- causality (relatedness to trial drug), in the opinion of the investigator
- whether the event would be considered expected.

Any change of condition or other follow-up information should be emailed/faxed to WCTU on the Serious Adverse Event Follow-Up form as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

The causality of SAEs (i.e. relationship to trial treatment) will be assessed by the investigator(s) on the SAE form.

Table 11 – SAE Causal relationship

Relationship to trial medication	Description
Unrelated	There is no evidence of any causal relationship
Unlikely to be related	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication or device). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible relationship*	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication or device). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable relationship*	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely related*	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

If there is a possible, probable or definite relationship to the intervention, then an assessment of expectedness must also be completed by the investigator(s) on the SAE form.

Section 4.8 of the SmPC relevant to the doxycycline/placebo will be used to assess expectedness of events. Up to date versions of the relevant SmPC will be monitored by WCTU

CERM Trial Team. Any updated SmPC will be sent to the MHRA for approval prior to use in the trial.

Causality and expectedness must be assessed by a clinical member of staff at the recruiting site who has been delegated this responsibility on the trial delegation log.

The CI or delegate will also review the SAE report to assess causality and expectedness. The CI or delegate will have the discretion to upgrade any events that require escalation, but will not be able to downgrade any clinical opinion made at site.

All SAEs assigned by the CI or delegate as both suspected to be related to IMP treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA).

SAE's deemed to be SUSARs will be reported to the REC/MHRA within the specified timelines according to UK legislation (i.e. 7 days for fatal/life threatening events and 15 days for other 'serious' categories).

WCTU will inform the Sponsor, MHRA and the REC of SUSARs within the required expedited reporting timescales.

The trial manager will liaise with the investigator to compile all the necessary information. Warwick CTU is responsible for reporting serious adverse events to the Sponsor, REC and MHRA within required timelines.

Participants are followed up throughout their pregnancy. Details of the trial follow-up duration are given in the CERM Trial summary table 5.

10.4 Responsibilities

Principal Investigator (PI):

Checking for AEs and ARs when participants attend for treatment / contacted for follow-up.

1. Using medical judgement in assigning causality and assessing severity. Grading each adverse event using CTCAE.
2. Assessing expectedness using the Reference Safety Information approved for the trial.
3. Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with WCTU if a record of receipt is not received within 2 working days of initial reporting.
4. Ensuring that AEs and ARs are recorded and reported to the sponsor in line with the requirements of the protocol.

Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning the SAEs seriousness and causality.

3. If related, assessing whether and event/reaction was expected in line with the Reference Safety Information
4. Immediate review of all SUSARs.
5. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
6. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

WCTU:

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a database.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
4. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines.
5. Notifying Investigators of SUSARs that occur within the trial.
6. The unblinding of a participant for the purpose of expedited SUSAR reporting.
7. Checking for (bi-annually) and notifying PIs of updates to the Reference Safety Information for the trial.
8. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

Trial Steering Committee (TSC):

In accordance with the trial TSC charter, periodically reviewing safety data and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC):

In accordance with the trial DMC charter, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

10.5 Notification of deaths

All deaths will be reported to the Sponsor irrespective of whether the death is related to the IMP, or an unrelated event.

10.6 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

10.7 Development safety update reports

WCTU will prepare and submit DSURs once a year throughout the clinical trial, or as necessary to the MHRA and REC. This report will detail any new safety data received during the reporting period. The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

11. TISSUE SAMPLES

11.1 Endometrial Biopsies

Endometrial biopsies will be sent to the central laboratory at University Hospitals Coventry and Warwickshire (UHCW) and should be collected, shipped and tracked in accordance with the CERM A Manual for collection of Endometrial Biopsies.

In some women taking the endometrial biopsy can be painful and may cause cramping at the time of the biopsy. Taking Paracetamol and Ibuprofen an hour before the biopsy can help with this. If needed gas and air (Entonox) is available while having the biopsy. In some women, spotting may happen after the biopsy is taken, this will resolve quickly on its own.

11.1.1 Analysis of endometrial biopsies

Once received UHCW laboratory will set the tissue sample in a wax block for analysis. Technicians preparing the biopsies will be competent to do so by virtue of their regular clinical work and will additionally be given training in the Standard Operating Procedure for the CERM Trial.

Guidance on the laboratory processing of tissue samples can be found in the CERM A Manual for processing, staining, analysis, and reporting of endometrial biopsy samples.

Chronic Endometritis will be diagnosed based on the density of CD138 staining cells within a tissue section. This methodology was derived from previously published material[36] and in advance of this trial it has been externally validated for the trial by experts in the field. The endometrial sample will be embedded in paraffin wax and sectioned onto slides. The slides will be stained with CD138 mouse monoclonal antibody. These will then be reviewed and the density calculated by trained observers following a standard operating procedure to ensure consistency. Borderline samples will be counted by two observers. The process will be both internally and externally quality assured as outlined in the trial document: CERM Trial: Analysis and Reporting of Endometrial Biopsy Samples Standard Operating Procedure. A positive screen will be defined as ≥5 CD138 positive cells per $10mm^2$. Samples will be reported as screen positive or negative to allow progression to randomisation. Exact counts will be kept to allow sub-group analysis of the data at a later stage.

Counting will be performed by trained members of the trial team who will have undergone an extensive training presentation and will be continually quality assured both internally and externally. Borderline samples will be counted by two separate observers. Technicians will follow the CERM A Manual for processing, staining, analysis, and reporting of endometrial biopsy samples.

11.1.2 Results of endometrial biopsy samples

Biopsy results will be emailed to sites within four weeks of receipt at the central laboratory.

11.2 Microbial swabs

For participants registered for CERM B a microbial swab of the vagina, endometrium and cervix will be taken and sent to Imperial College London for analysis in special containers.

Clinicians taking swabs will be competent to do so either by virtue of clinical role and training or appropriate specialist training on the technique for the trial. Clinicians will follow the CERM B Manual for collection of Microbial Swabs.

11.2.1 Analysis of the microbiome

Vaginal, endometrial and cervical swabs before and after treatment will be sent to Imperial for exploratory analysis of the endometrial microbiome. These paired samples will be labelled with:

- Trial ID number
- first or second sample
- Treatment allocation – Imperial researchers will only be told treatment allocation at the end of the trial.

Details of the preparation of the swabs and analysis is in the SOP for microbiome analysis. Microbiologists undertaking the analysis of swabs will be doing so commensurate with their role having previously undergone relevant training in the area.

In some cases there may be tissue left over, with the women's permission, we will keep this tissue for future research studies into pregnancy loss. The tissue will be stored anonymously in the Tommy's reproductive health bio-bank and kept strictly in accordance with The Human Tissue Act 2004.

12. STATISTICS AND DATA ANALYSIS

12.1 Sample size

12.1.2 Sample size – screening trial

The target sample size for the screened participants is 3,062.

12.1.3 Sample size - randomised controlled trial

The target sample size is 1,500, 750 women in the intervention arm (doxycycline) and 750 women in the control arm (placebo).

The total number of women recruited to the screening part of trial will be determined by the proportion eligible for the randomised controlled trial. Our current assumptions suggest as overall recruitment of around 3,062 women over 24 months with 1,500 women in the randomised trial.

In simulations, we have used a maximum sample size of 1,500, and a maximum recruitment rate of 16 women/week from all centres. We have used four interim analyses, after 250, 500, 750 and 1000 women have been recruited, with the following stopping rules: stopping for futility/harm if the predictive probability of obtaining $p<0.025$ if the trial continued to its full sample size is less than 0.01, and stopping for established efficacy if the probability that the intervention is better than control is greater than 0.99. We assumed that 24% of women would get pregnant every month, giving an overall proportion achieving pregnancy by six months of 80%, and that the 12-week outcome would be known between 16 and 36 weeks after randomisation. The performance of this design was good in two treatment effect scenarios. With no difference between the intervention and control groups, 71.4% of trials stopped early for futility (correctly), and 1.2% stopped early for success (Type I error). The average sample size was 1193, and the average duration was 130 weeks (recruitment and follow-up). With the target treatment effect (48% control, 56% intervention), 54.8% stopped early for success, and an additional 33.4% did not stop early but found probability of benefit to the intervention group of >95%, giving an overall probability of correctly identifying benefit (power) of 88.2%. Average sample size was 1,247 and duration was 133 weeks.

12.2 Stratification

Randomisation: Women will be randomised to placebo or doxycycline. Minimisation will be by age (<35 vs ≥35 years) and number of previous miscarriages (≤3 vs >3) as these are the two most important predictors of pregnancy outcome in women with RM.

12.3 Statistical analysis

The primary analysis will be conducted by intention to treat (ITT). The treatment difference will be compared between the participants randomised to placebo and doxycycline. The primary outcomes, on-going pregnancy at 12 weeks and total live births, will be analysed using logistic regression models.

Secondary analysis will be conducted in a similar approach. The treatment effect will be compared to assess the categorical and continuous secondary outcomes using logistic and linear models, respectively.

Mediation analysis will be carried out to investigate whether any treatment effect on the total number of live births is mediated by conception, early miscarriage, or late miscarriage.

The results will be reported as odds ratio (OR) with 95% confidence interval (CI) for categorical outcomes and mean difference with 95% CI for continuous outcomes. The analysis will be conducted in an unadjusted and adjusted way, with adjustment for the stratification variables and important covariates. Missing data for the primary outcomes are likely to be minor. However, if the missing primary outcome data exceeds 20%, imputation techniques will be employed and the imputed data will be used as a sensitivity analysis.

Treatment effect will also be assessed in the following subgroup for exploratory purpose:

- Age (<35 vs ≥35)
- Severity of chronic Endometritis:
    - Negative (0-4 CD138 cells)
    - Mild (5-20 CD138 cells)
    - Moderate (21-200 CD138 cells)
    - Very high (201+ CD138 cells)
- number of previous miscarriages (≤3 vs >3)

The interaction between the subgroup variable with treatment will be tested and the overall significance of the interaction will be reported.

12.3.1 Interim analysis

Adaptive trial approach using the on-going pregnancy rate for efficient trial design Instead of a fixed trial design, we will use interim analyses to look at the data during recruitment and allow early stopping if it is likely that the trial will be inconclusive, or it is already clear that the intervention is effective or harmful.

The trial will stop early if, based on data at any interim analysis, it is either very unlikely that a positive result would be obtained, or efficacy or harm has already been convincingly demonstrated. These planned interim analyses will act as clear milestones for the trial. In simulations, we have used a maximum sample size of 1,500, and a maximum recruitment rate of 15 women/week from all centres. We have used four interim analyses, after 250, 500, 750 and 1000 women have been recruited, with the following stopping rules: stopping for futility/harm if the predictive probability of obtaining $p<0.025$ if the trial continued to its full sample size is less than 0.01, and stopping for established efficacy if the probability that the intervention is better than control is greater than 0.99. We assumed that 24% of women would get pregnant every month, giving an overall proportion achieving pregnancy by 6 months of 80%, and that the 12-week outcome would be known between 16 and 36 weeks after randomisation. The performance of this design was good in two treatment effect scenarios. With no difference between the intervention and control groups, 71.4% of trials stopped early for futility (correctly), and 1.2% stopped early for success (Type I error). The average sample size was 1193, and the average duration was 130 weeks (recruitment and follow-up). With the target treatment effect (48% control, 56% intervention), 54.8% stopped early for success, and an additional 33.4% did not stop early but found probability of benefit to the intervention group of >95%, giving an overall probability of correctly identifying benefit (power) of 88.2%. Average sample size was 1,247 and duration was 133 weeks.

A detailed statistical analysis plan (SAP) will be developed by the trial statistician and approved in line with the WCTU SOP requirements.

13. DATA MANAGEMENT

Personal data collected during the trial will be handled and stored in accordance with the General Data Protection Regulation (GDPR) and Data Protection Act 2018. UHCW and WCTU at the University of Warwick (UoW) will act as joint data controllers for this trial. UHCW, UoW and Imperial College London will also act as Data Processors (as defined in GDPR).

13.1 Data collection tools and source document identification

13.1.1 Database

The database will be developed by the Programming Team at WCTU. All specifications (i.e. database variables, validation checks, screens) will be agreed between the programmers and appropriate WCTU trial staff and the trial sponsor. The electronic case report forms (eCRFS) will be designed by the Chief Investigators, Trial Manager, Medical Statistician, Programmers, Senior Research Fellow and representatives from obstetric units.

13.1.2 eCRF completion

CERM will use a remote electronic data capture system. All data will be directly entered onto eCRFs in the trial database by site staff from the source data (e.g. hospital records, participant medical notes, laboratory records and clinical reports). Data can only be entered by staff who are listed on the site staff delegation log and authorised by the PI to perform this duty. All data submitted on eCRFs must be verifiable in the source documentation. Any deviation from this must be explained appropriately.

When collecting data during verbal conversations with participants, please ensure that relevant details of the conversation are fully detailed in source documents. This will enable the corresponding eCRF data to be verified against the source documents. If an inconsistency is identified between data obtained during verbal discussions and data in existing source documents, details of the discrepancy should be documented with a clear justification for which source is deemed accurate.

13.1.3 Missing data

All fields MUST be completed. If data is unavailable because a test or measurement was not done, please indicate why that was omitted on the eCRF. Data should be corrected at site if any errors are made. Upon correcting data staff will be asked to specify the reason for the correction. An explanatory note should be added if necessary.

13.1.4 Timelines for eCRF completion

eCRFs must be completed in a timely manner as soon as possible after the trial visit/assessment. Procedures for chasing missing eCRFs and data will be detailed in the CERM Data Management Plan.

13.1.5 Data quality

Data entered into the trial database will be checked for accuracy and completeness in accordance with the trial data management plan.

13.1.6 Post randomisation withdrawals and exclusions

In accordance with the Declaration of Helsinki, each participant is free to withdraw from the research trial at any time (including follow-up) without providing a reason and without prejudice, if they so wish. Women are informed of their rights in the participant information sheet. Unless a woman explicitly withdraws their consent, they and their infant will be followed-up wherever possible and data collected as per the protocol until the end of the trial. Should a women decide to withdraw after randomisation, after the intervention or should the investigator(s) decide to withdraw the participant, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible.

The reason for withdrawal will be recorded in the Case Report Form (CRF). If the reason for withdrawal is an Adverse Event (AE), monitoring of the participant and infant will continue until the outcome is evident. The specific event will be recorded in a CRF.

If participants deliver their baby in a different trust to the trust they were consented at, please contact the research team at the relevant NHS organisation to obtain medical details in relation to this research trial.

13.2 Data handling and record keeping

All data will be stored securely and held in accordance with the relevant UK data protection legislation. Data will be entered on-line onto the secure password protected trial data base and accessible only by authorised members of the team.

Participant identification data will be required for the registration process. WCTU will preserve the confidentiality of participants taking part in the trial.

Participant confidentiality will be ensured by using a trial identification number to identify a participant. Sites will maintain a participant enrolment log linking the participant's name to their trial identification number. This list will only be accessible to authorised members of the trial team. Participant case notes and files may be inspected by members of WCTU, Sponsor and other regulatory bodies as required (written consent for this will be sought as part of the informed consent process).

Any data or samples transferred from the site will be identified by the trial identification number only.

Participants will not be identified in any trial reports or publications.

13.3 Access to data

All trial related documentation will be stored in accordance with all applicable regulatory requirements and access restricted to authorised personnel.

Participant data at the offices of WCTU will be kept in individual participant files (identified only by trial identification number) in filing cabinets in locked offices accessible only to authorised members of the CERM trial team.

Access to the databases will be restricted to authorised personnel only including representatives from WCTU, the sponsor and the regulatory authorities to permit trial-related monitoring, audits and inspections - in line with participant consent.

13.4 Data archiving

Following the resolution of queries and confirmation of trial close-out by the Chief Investigator the trial records and associated documentation held at WCTU for all women registered into the CERM trial will be archived for 25 years. Data will be archived in accordance with WCTU SOP 23 'Data Archiving'.

At site the PI or designee must maintain adequate and accurate records to enable the conduct of the Trial to be fully documented and the Trial data to be subsequently verified. After trial closure the PI will maintain all source documents and trial related documents. All source documents will be retained for a minimum period of ten years following the end of the Trial. WCTU will authorise and advise of the archiving requirements as part of the site closure process (on behalf of the Sponsor).

14. TRIAL OVERSIGHT

14.1 Role and responsibilities of the Sponsor

University Hospitals Coventry and Warwickshire NHS Trust, Clifford Bridge Road, Coventry CV2 2DX, will act as Sponsor for the trial and undertake the responsibilities as defined by the UK Policy Framework For Health and Social Care Research and ICH Good Clinical Practice. An authorised representative of the Sponsor has approved the final version of this protocol with respect to the trial design, conduct, data analysis and interpretation and plans for publication and dissemination of results.

Trial management will be undertaken at Warwick Clinical Trials Unit, the University of Warwick, Coventry, CV4 7AL. A sub-contract agreement is in place between UHCW and WCTU who will provide full research management services. This will specify whose SOPs will be adhered to for each aspect of the trial.

Clinical Trial Agreements will also be in place between the Sponsor and each research site, with clear delegation of roles and responsibilities.

14.1.1 Indemnity

'NHS indemnity covers NHS staff, medical academic staff with honorary contracts and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk. Negligent harm cover will be provided by standard NHS arrangements. NHS Indemnity does not give indemnity for compensation in the event of non−negligent harm, so no specific arrangements exist for non−negligent harm for this trial'. The University of Warwick Clinical Trials Unit has a Clinical Trials Insurance Policy, Professional indemnity and legal liability insurance in place to cover the CERM trial.

14.2 Role and responsibilities of the Funder

Funding for this trial is provided by the Efficacy and Mechanism Evaluation Programme (EME) which is within the National Institute for Health Research (NIHR). The design and management of this trial are entirely independent of the funder.

14.3 Trial management arrangements

14.3.1 Trial Management Group

The Trial Management Group (TMG) comprises co-investigators, allied experts and trial management staff and is responsible for the day-to-day running of the trial (Table 1). Significant issues that may arise will be reported by the Chair to the Trial Steering Committee and / or Data Monitoring Committee (DMC) and the Sponsor. The TMG will meet monthly throughout the trial and will invite key staff from collaborating and external organisations and investigators from participating sites as required.

The TMG Charter will specifically detail the membership, responsibilities and purpose of the TMG.

14.3.2 Trial Steering Committee

The Trial Steering Committee (TSC) comprises independent lay members, experts in biostatistics, health and clinical epidemiology and obstetrics and gynaecology (Table 2). The TSC will approve the final trial protocol, advise on all aspects of the trial conduct, monitor trial progress, review relevant information from other sources, consider recommendations from the DMC and advise on protocol amendments. They will assess recruitment after 250 patients have been randomised, and will consider modification or termination of the trial (in consultation with the DMC) in the event of poor recruitment. They will meet regularly throughout the trial and not less than once a year.

The TSC Charter will specifically detail the membership, responsibilities and purpose of the TSC.

14.3.3 Data Monitoring Committee

The Data Monitoring Committee (DMC) comprises independent experts with relevant clinical research, and statistical experience. (Table 3). They will ensure close monitoring of outcomes and safety aspects during the trial.

Confidential reports containing recruitment, protocol compliance, safety data and interim assessments of outcomes will be reviewed by the DMC. The DMC will advise the TSC as to whether there is evidence or reason why the trial should be amended or terminated.

DMC meetings will also be attended by the Chief Investigator and Trial Manager (for non-confidential parts of the meeting) and the trial statistician. They will meet regularly throughout the trial and not less than once a year.

The DMC Charter will specifically detail the membership, responsibilities and purpose of the DMC.

14.3.4 Investigator meetings

Investigator meetings will be held during recruitment and key staff from participating sites will be invited. The meetings will review trial progress, recruitment and discuss any emerging issues.

14.3.5 Essential documentation

A Trial Master File will be set up in accordance to WCTU SOP 11 - 'Essential Documentation' and held securely at WCTU. Investigator Site Files and pharmacy files will be prepared and distributed to participating trial sites by WCTU.

14.3.6 Warwick CTU CERM trial team

Warwick Clinical Trials Unit CERM trial team will have responsibility for overseeing day to day coordination of the trial and reporting regularly to the TSC. The WCTUs trial management responsibilities include, but are not limited to:

- Coordinating protocol development, participant and trial management documents

- Correspondence with trial funder and tracking of progress against agreed milestones
- Setting up and maintaining the Trial Master File;
- Ensuring necessary approvals are in place before the start of the trial at each site;
- Submitting amendments to the MHRA and REC and disseminating these to sites
- Providing training to trial personnel;
- Providing data management support; including data input, maintenance of the trial database and raising of queries
- Producing trial progress reports and coordinating TSC meetings and minutes;
- Ensuring data security and quality and ensuring data protection laws are adhered to;
- Ensuring complete records are in place for audit and monitoring purposes;
- Ensuring the trial is conducted in accordance with the ICH GCP;
- Monitoring, recording, reporting and resolving any non-compliance with the protocol or GCP
- Archiving all original trial documents including the data forms in line with WCTU SOPs"

15.4 Trial registration

The trial's International Standard Randomised Controlled Trial Number is [TBC] and EudraCT number is 2019-000585-38.

15. MONITORING, AUDIT & INSPECTION

The trial will be monitored and audited by Warwick Clinical Trials Unit, as representatives of the sponsor, in accordance with WCTU procedures to ensure that the trial is being conducted as per protocol, adhering to Research Governance and GCP. The Sponsor will perform a co-monitoring visit at their own site UHCW.

The approach to, and extent of, monitoring will be specified in a trial monitoring plan determined by the risk assessment undertaken prior to the start of the trial.

15.1 Training

The Chief Investigator has completed chief investigator training course and courses on handling and storing of human tissue.

A programme of trial specific training will be provided to all clinicians, staff participating in the trial, and PPI as required including: the principles of Good Clinical Practice, the importance of the trial, background, the trial protocol, inclusion and exclusion criteria, ethical issues and consent, randomisation procedures, data collection, documentation and completing and maintaining training logs. All training information and materials will be available via the trial website (https://warwick.ac.uk/cerm). All new staff will complete a trial induction and training programme. PPI members will also be offered a place on the CTU training day entitled '*Being Part of a Research Team*' https://warwick.ac.uk/ppitrianing.

15.2 Quality assurance

A risk assessment will be undertaken and will form the basis of the trial monitoring plan. Sites will be visited during the recruitment period to audit the quality of the trial process and documentation. Additional site visits may be required, if triggered by issues raised as documented in the monitoring plan.

15.3 Visits to sites

The trial will be monitored and audited in accordance with WCTU procedures. All trial related documents will be made available on request for monitoring and audit by WCTU, UHCW, REC and for inspection by the MHRA or other relevant bodies. Prior to the trial start, the PI will be advised of the anticipated frequency of the monitoring visits. The PI and site R&D department (if applicable), will receive reasonable notification prior to each monitoring visit.

During an on-site monitoring visit the WCTU monitor/trial manager will review trial records and compare them with source documents, discuss the conduct of the trial and any emerging problems with the PI (or designee), check that the drug storage, dispensing and retrieval are reliable and appropriate and verify that the available facilities remain acceptable.

The PI will allow WCTU direct access to relevant source documentation for verification of data entered onto the CRFs taking into account data protection regulations. Entries in the CRF will be compared with participants' medical records and the results will be documented in a monitoring report form. The WCTU monitor/trial manager should also be given access to

other relevant departments (i.e. pharmacy) and relevant trial staff should be available to meet as required.

The participants' medical records and other relevant data may also be reviewed by appropriate qualified personnel independent from the WCTU appointed to audit the trial, and by regulatory authorities. Details will remain confidential and participants' names will not be recorded outside the hospital.

Following a monitoring visit the WCTU monitor/trial manager will send a copy of the monitoring report to the PI at site, other relevant trial staff and the trial Sponsor. The PI will be given appropriate time to provide a written response to the findings listed on this report. The response will be considered by the Sponsor to determine if adequately addresses the issues identified.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Ethical approval and research governance

The trial will be conducted in full conformance with the principles of the Declaration of Helsinki, ICH Good Clinical Practice (GCP) guidelines and the UK Statutory Instrument Number 1031 that implements the Medicine for Human Use (Clinical Trials) Directive 2004 and subsequent amendments. All data will be stored securely and held in accordance with Data Protection Act 2018.

This trial will seek a Clinical Trial Authorisation from the UK Competent Authority the Medicines and Healthcare products Regulatory Agency (MHRA), favourable opinion from a Research Ethics Committee and Health Research Authority (HRA) approval. All required ethical and regulatory approval(s) for the trial will be sought using the Integrated Research Application System. The CERM trial is part of the HRA and MHRA combined ways of working pilot. Before enrolling participants into the trial, capacity and capability assessment and approval from each relevant NHS Trust Research & Development (R&D) departments must be obtained by the Warwick Clinical Trials Unit CERM Trial Team and an official site opening letter issued.

Substantial protocol amendments will be provided to Principal Investigators and site staff and other relevant parties once the appropriate approvals have been obtained.

Annual reports will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The REC and the MHRA will be notified of the end of the trial (whether at planned time or prematurely).

The Chief Investigator will submit a final report to the required authorities with the results, including any publications within one year of the declared end of the trial.

16.2 Ethical considerations for women participating in CERM

In any trial involving women trying to conceive, consideration is needed on the ethical aspects of the trial. In this trial there is a paradox; to help women to have a baby we are asking them to use contraception for up to four menstrual cycles: biopsy preparation, biopsy, screening and if they screen positive, randomisation (figure 4). This may be a difficult decision, considering the majority of women will not receive active medication, and especially difficult for women with sub-optimal fertility. Therefore it is important to minimise the time women are using contraception by streamlining the participant journey and trial processes.

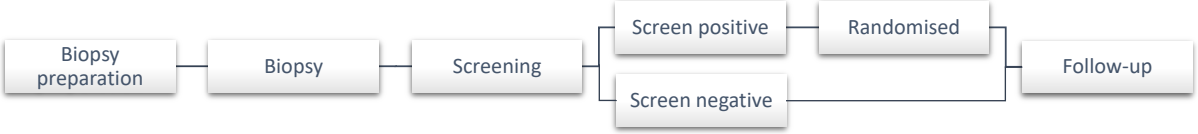

Figure 4 – CERM participant journey

If a women reports unprotected sexual intercourse or a condom failure, in the month prior to her biopsy, the biopsy will be cancelled and she will have to wait for her next menstrual cycle

and prepare for the biopsy again; If this happens it will further delay conception and this may be distressing and or frustrating for some women. If a women conceives following unprotected sexual intercourse or a condom failure she will follow the pregnancy care pathway and be referred to her GP who will arrange her care.

Women who screen negative for CE may be disappointed that a possible cause for their RMs has not been identified. They will return to the usual care pathway but if they have consented at screening they will be contacted and data will be collected on any first pregnancies within 12 months of their negative CE diagnosis.

To try to reduce distress and or frustration and ensure the risks are clearly stated our PPI co-applicant is leading on the development of all participant facing materials, together with the research team.

The participant information sheets and participant information leaflet, have been reviewed and revised by editors from the Plain English Campaign and they have all received a Crystal Mark. We will also develop a web-based resource for women with more detailed information available from the trial website https://warwick.ac.uk/cerm.

Women will be given as much time as they need to consider participating in the trial and have the opportunity to discuss participation and ask questions with specially trained clinicians including obstetricians, research midwifes and unit midwifes.

We will ensure that all identifiable data is anonymised and treated as confidential. All data will be stored securely and held in accordance with all applicable UK legislation and WCTU Standard Operating Procedures (SOPs).

16.3 Notification of Serious Breaches to GCP and/or the protocol

"A 'serious breach' will be defined as a deviation from the protocol or GCP that is likely to effect to a significant degree:

1. The safety or physical or mental integrity of the subjects of the trial; or
2. The scientific value of the trial

WCTU will be notified immediately of any case where the above definition applies during the trial conduct phase. In accordance with the WCTU SOP 31 'Deviations, Violations, Misconduct and Serious Breaches of GCP and/or Study Protocol' WCTU will notify the licensing authority in writing of any serious breach of:

1. The conditions or principles of GCP in connection with the trial; or
2. The trial protocol, as amended time to time, within 7 days of becoming aware of the breach

16.4 Patient and Public Involvement

16.4.1 The Lily-Mae Foundation

The Lily-Mae Foundation (https://www.lilymaefoundation.org), a leading charity supporting parents and families after pregnancy loss. A co-founder of the charity is a co-applicant and

has been involved in the planning and development of this trial. They will be involved in all aspects of trial management and attend monthly TMG meetings. They will lead on the development of all the patient facing materials including the patient information sheets, patient information booklet, consent forms, trial poster and the content of the participant area of the trial website. This will ensure the clarity of the information given to participants.

16.4.2 The Tommy's Charity

A PPI member from the Tommy's Charity and Miscarriage Association will sit on the TSC.

A training course will be provided for PPI members to cover all trial related activities (https://warwick.ac.uk/ppitraining).

17. DISSEMINATION AND PUBLICATION

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the WCTU CERM Trial team and the final version will be agreed by the wider Trial Management Group before submission for publication.

The proposed trial will determine if a pre-pregnancy course of doxycycline in women with CE prevents miscarriage. If this is the case, implementation into clinical practise will be rapid as the diagnosis is based on endometrial biopsy, which is a routine outpatient procedure, the intervention (doxycycline) is inexpensive, widely used and safe antibiotic and there are currently few effective interventions to prevent miscarriage.[23] The trial will also determine the effects of doxycycline on the microbiome, and its effect on decidualisation and pregnancy outcome.

The results will be available to women, their partners, heath care professionals and policy makers via the Tommy's website (https://www.tommys.org), social media, publications in open access journals, clinical practice guidelines (e.g. Royal College of Obstetricians and Gynaecologists, European Society of Human Reproduction and Endocrinology, National Institute for Health and Care Excellence (NICE)), conference presentations and via a trial webpage to be hosted on Warwick Medical School (https://warwick.ac.uk/cerm).

The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org).[37] Authorship of all trial publications will be agreed in accordance with the WCTU SOP 22 'Publication and Dissemination'.

All publications will be submitted to the NIHR-EME Programme for approval prior to submission for publication.

Links to all findings, reports, publications and events will be available via the trial website (https://warwick.ac.uk/cerm).

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