

MifeMiso

**Mifepristone and misoprostol versus misoprostol
alone in the medical management of missed
miscarriage: the MifeMiso randomised
controlled trial**

Appendix III: Final trial protocol



A randomised placebo-controlled trial of mifepristone and misoprostol versus misoprostol alone in the medical management of missed miscarriage

Protocol Version 5.0 (27th June 2019)



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1. Introduction

The MifeMiso trial is a double blind, placebo-controlled trial to test the hypothesis that treatment with mifepristone plus misoprostol is superior to misoprostol alone for the resolution of miscarriage within 7 days in women diagnosed with missed miscarriage by pelvic ultrasound scan in the first 13+6 weeks of pregnancy.

Should the MifeMiso trial demonstrate a benefit from the intervention, it would provide important evidence for the combined use of these treatments for the timely resolution of miscarriage.

In order to recruit the required number of women needed to provide statistically reliable answers, and to maximise the clinical relevance of the findings, the trial is designed to fit in with routine hospital practice as far as possible, imposing minimal additional workload by keeping extra clinic-based tests and evaluations to a minimum.

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1.1.4 Summary and Declarations

Protocol Version	5.0 (27-Jun-2019)
Protocol Version	4.0 (09-Feb-2018)
Protocol Version	3.0 (01-Mar-2017)
Protocol Version	2.0 (27-Jan-2017)
Previous Version	1.0 (11-Nov-2016)

Protocol Amendments				
The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.				
Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
1	01/03/2017	3.0	Substantial	<i>Addition of ISRCTN and Clinical Trials.gov number. Clarification regarding emergency unblinding, rationale for using stated doses of mifepristone and misoprostol, amendment to statements regarding assessment of severity and causality of SAEs, clarification regarding vaginal bleeding as an event not reportable as an SAE, 'resolution of miscarriage' amended to 'discharge' in table 5, clarification that day 21 ± 2 is the point of discharge for women with a negative pregnancy test result, clarification regarding additional EQ-5D-5L questionnaire to be completed by women with an initial positive pregnancy test result, clarification regarding compliance monitoring, primary and secondary endpoint analyses</i>
2	09/02/2018	4.0	Substantial	<i>Change of contact details for trial personnel, clarification of primary and secondary outcomes, addition of sublingual route for misoprostol</i>

				<p><i>administration, clarification on trial flowchart that repeat scan at day 6-7 not required if scan performed earlier than this time point and sac has passed, clarification that the screening log is accessible through the online randomisation system, clarification of storage temperature for IMP, clarification of ways in which CSQ-8 questionnaire (satisfaction survey) is administered i.e paper and electronic, addition of 'previous participation in the MifeMiso trial' and 'woman not able to attend for day 6-7 ultrasound scan' to list of exclusion criteria, clarification of the end of trial definition, clarification that qualitative interviews may be conducted via video call software e.g. Skype</i></p>
3	27/06/2019	5.0	Substantial	<p><i>Update to trial team contact details, update to secondary outcomes and objectives, reclassification of some secondary outcomes as safety outcomes, clarification regarding unblinding, update to health economic evaluation section, addition of section regarding Blinded Endpoint Review Committee, update to statistical analysis section</i></p>

ISRCTN 17405024

EudraCT Number 2016-005097-35

ClinicalTrials.gov Number NCT03065660

Funding Body NIHR Health Technology Assessment (HTA) Programme grant number 15/160/02

Sponsor University of Birmingham

Chief Investigator Professor Arri Coomarasamy

The University of Birmingham is responsible for obtaining the necessary regulatory approvals and for pharmacovigilance. The Trial Management Group (TMG) is jointly responsible for overseeing Good Clinical Practice (GCP). The investigators are responsible for obtaining informed consent and care of the participants.

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

Chief Investigator's signature

Professor Arri Coomarasamy

Date:

Chief Investigator on behalf of the Trial Management Group

Sponsor statement:

Where the University of Birmingham takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.

1.1.5 Principal Investigator's signature page

Site:

Title: A randomised placebo-controlled trial of mifepristone and misoprostol versus misoprostol alone in the medical management of missed miscarriage (MifeMiso trial)

Version 5.0

I confirm I have received, read and understood the aforementioned version of the trial protocol. I confirm my team and I will adhere to this version of the protocol following receipt of the required local approvals.

Principal Investigator's name: _____

Signature: _____

Date: dd / mmm / yyyy

The Principal Investigator should sign and date this page and return a copy to the
MifeMiso Trial Office

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1.2 Definitions

Term	Description
Policies	Policies are developed to describe the approach of the UoB on areas that are heavily regulated. Policies may also be developed when there is ambiguity in how regulatory requirements should be implemented in the QMS or when procedures to be captured in the QMS address areas controversial within the UoB at the time of implementation. Policies explain why the UoB has its procedures, especially when they seem to deviate from the regulatory requirements. Policies should be read in conjunction with the relevant SOP. Policies that are not part of a Quality Manual are coded up as 'POL'.
QCD	See "Quality Control Documents"
QMS	Quality Management System
Quality Control Documents (QCD)	Quality Control Documents can be instructions, forms, templates or checklists. They are developed to share best practices, promote standardisation to guarantee quality standards are maintained and reduce resources otherwise needed to develop similar documents. Unless indicated otherwise in the relevant SOP, QCDs are not mandatory and are designed to be an optional aid to UoB staff.
Quality Management System (QMS)	A Quality Management System (QMS) is a system that includes procedures and policies to describe how certain tasks should be performed and that encapsulate any standards and/or regulatory requirements that may apply to those tasks. By adhering to the Quality Management System, the user and the UoB will be assured that applicable regulations are adhered to.
SOP	See "Standard Operating Procedures"
Standard Operating Procedures (SOP)	Standard Operating Procedures are detailed written instructions to achieve uniformity in the performance of a specific function. They define tasks, allocate responsibilities, detail processes, indicate documents and templates to be used and cross-reference to other work instructions and guidance or policy documents. They are standards to which the UoB may be audited or inspected.
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Adverse Reaction (AR)	All untoward and unintended responses to an IMP related to any dose administered.
Serious Adverse Event (SAE)	Any untoward medical occurrence or effect that: <ul style="list-style-type: none"> • Results in death • Is life-threatening* • Requires hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • Or is otherwise considered medically significant by the Investigator**

	<p>* Life threatening in the definition of an SAE 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 that hypothetically might have caused death if it were more severe.</p> <p>** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.</p>
Serious Adverse Reaction (SAR)	An Adverse Reaction which also meets the definition of a Serious Adverse Event
Unexpected Adverse Reaction (UAR)	<p>An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product).</p> <p>When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.</p>
Suspected Unexpected Serious Adverse Reaction (SUSAR)	<p>A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information.</p> <p>A SUSAR should meet the definition of an AR, UAR and SAR.</p>
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

1.3 Abbreviations

AE	Adverse Event
AR	Adverse Reaction
BCTU	Birmingham Clinical Trials Unit at the University of Birmingham
BERC	Blinded Endpoint Review Committee
BMI	Body Mass Index
CI	Chief Investigator
CTA	Clinical Trial Authorisation
DMC	Data Monitoring Committee
EPAU	Early Pregnancy Assessment Unit
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GP	General Practitioner
HTA	Health Technology Assessment
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
LCRN	Local Clinical Research Network
MHRA	Medicines and Healthcare Products Regulatory Agency
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PI	Principal Investigator (leading local investigator for the MifeMiso study)
PIS	Participant Information Sheet
RCOG	Royal College of Obstetricians and Gynaecologists
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

1.4 Trial synopsis

Title	A randomised placebo-controlled trial of mifepristone and misoprostol versus misoprostol alone in the medical management of missed miscarriage
Acronym	MifeMiso
Objectives	<p>Primary objective:</p> <p>To test the hypothesis that treatment with mifepristone plus misoprostol is superior to misoprostol alone for the resolution of miscarriage within 7 days in women diagnosed with missed miscarriage by pelvic ultrasound scan in the first 13+6 weeks of pregnancy.</p> <p>Key secondary objective:</p> <p>To test the hypothesis that the addition of mifepristone reduces the need for surgical intervention to resolve the miscarriage.</p> <p>Other secondary objectives:</p> <ol style="list-style-type: none"> 1. To evaluate if the addition of mifepristone reduces the need for further doses of misoprostol. 2. To evaluate if the addition of mifepristone improves other clinical outcomes including surgical intervention up to and including 7 days post-randomisation and after 7 days post-randomisation, duration of bleeding, infection, negative pregnancy test at 21 days post-randomisation, time from randomisation to discharge from EPU care, side effects and complications. 3. To evaluate if the addition of mifepristone improves patient satisfaction 4. To assess the cost-effectiveness of the combination of mifepristone and misoprostol in the medical management of missed miscarriage.
Trial Design	A randomised, parallel group, double-blind, placebo-controlled multicentre study, with health economic and mixed-methods evaluation.
Setting	Early pregnancy units and gynaecology departments.
Number of Participants	We plan to randomise 710 women in total (355 participants each in the mifepristone and placebo arms).

Main Eligibility Criteria	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> • Women diagnosed with missed miscarriage by pelvic ultrasound scan in the first 13+6 weeks of pregnancy that choose to have medical management of miscarriage. • Age 16 years and over. • Willing and able to give informed consent. <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> • Women opting for alternative methods of miscarriage management (expectant or surgical) • Diagnosis of incomplete miscarriage. • Life threatening bleeding. • Contraindications to mifepristone or misoprostol use for example chronic adrenal failure, known hypersensitivity to either drug, haemorrhagic disorders and anticoagulant therapy, prosthetic heart valve or history of endocarditis, existing cardiovascular disease, severe asthma uncontrolled by therapy or inherited porphyria. • Current participation in another blinded, placebo-controlled trial of investigational medicinal products in pregnancy. • Previous participation in the MifeMiso trial • Woman not able to attend for day 6-7 ultrasound scan
Study Interventions	<p>A single dose of oral mifepristone 200mg, followed by a single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later, will be compared with an oral placebo tablet followed by a single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later.</p> <p>The 800mcg dose of misoprostol is justified by NICE guidance CG154.</p>
Duration of Study	<p>It is anticipated that the trial will last for three years.</p>
Randomisation	<p>Participants will be randomised on-line via a secure internet facility in a 1:1 ratio through a third party independent Integrated Trial Management System (MedSciNet Clinical Trial Framework).</p> <p>A “minimisation” procedure using a computer-based algorithm will be used to avoid chance imbalances in the following important variables:</p> <p>Maternal age (<30, ≥30 years), body mass index (<35, ≥35 kg/m²), previous parity (nulliparous, parous women), gestational age (<70, ≥70 days), amount of bleeding (PBAC score; ≤2, ≥3) and randomising centre.</p>
Outcome Measures	<p>Primary Outcome:</p> <p>Failure to spontaneously pass the gestational sac within 7 days after randomisation</p> <p>Key Secondary Outcome:</p> <p>Surgical intervention to resolve the miscarriage (collected up to discharge from EPU care)</p> <p>Other Secondary Outcomes:</p> <p>Surgical intervention to resolve the miscarriage up to and including day 7 post-randomisation Surgical intervention to resolve the miscarriage after day 7 post-randomisation to discharge from EPU care Need for further doses of misoprostol up to day 7 post-randomisation Need for further doses of misoprostol up to discharge from EPU care Overall patient satisfaction score (measured using the CSQ-8 questionnaire and collected upon discharge from EPU care).</p>

	<p>Patient quality of life (Index value and overall health status measured using the EQ-5D-5L questionnaire and collected on date of randomisation, day 6-7 post-randomisation or day of follow-up USS if different to day 6-7 and day 21 +/- 2 days post-randomisation. If a woman obtains an initial positive pregnancy test result at day 21 +/- 2 days post-randomisation then a further EQ-5D-5L questionnaire is collected upon discharge from EPU care).</p> <p>Duration of bleeding reported by woman (days) (collected up to discharge from EPU care)</p> <p>Diagnosis of infection associated with miscarriage requiring outpatient antibiotic treatment (collected up to discharge from EPU care)</p> <p>Diagnosis of infection associated with miscarriage requiring inpatient antibiotic treatment (collected up to discharge from EPU care)</p> <p>Negative pregnancy test result 21 days (\pm 2 days) after randomisation.</p> <p>Time from randomisation to discharge from EPU care (described using summary statistics only)</p> <p>Safety Outcomes:</p> <p>Blood transfusion required (collected up to discharge from EPU care)</p> <p>Side effects (collected up to discharge from EPU care)</p> <p>Death (collected up to discharge from EPU care)</p> <p>Any serious complications (collected up to discharge from EPU care)</p> <p>Resource Use Outcomes:</p> <p>Outpatient or emergency visits; inpatient admissions (nights in hospital); need for further doses of misoprostol; need for surgical intervention.</p> <p>Mixed-methods Evaluation Outcomes:</p> <p>We will undertake a quantitative patient satisfaction survey with all women recruited, using a validated and well-established eight item Client Satisfaction Questionnaire (CSQ-8). The results from this survey will be used as a sampling frame via which we will purposively sample those participants who were satisfied/found the service acceptable, and those who did not, for a semi-structured interview to explore their experiences in more detail.</p> <p>Outcomes for Future Studies:</p> <p>We will obtain women's consent for future evaluation of themselves and any subsequent pregnancies using their health records. Although long-term follow-up will remain outside the scope of this trial, we plan to conduct further studies on outcomes such as subsequent successful pregnancies post-miscarriage resolution.</p>
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2 Background

2.1 Clinical background

Miscarriage is common (20% of pregnancies; approximately 125,000 miscarriages per year in England) (1). Miscarriage is associated with not only physical harm, such as excessive bleeding, infection, and uterine perforation during surgery, but also substantial psychological impact on patients; studies have shown that distress from miscarriage is equivalent to that from stillbirth of a term baby (2) and miscarriage is estimated to cost the NHS £81 million per year (3). Management of miscarriage can be expectant (waiting for natural miscarriage), medical (with drugs) or surgical. A UK survey conducted by this study team has shown that 24% of women opt for medical management (see section 2.1.2). However, there is uncertainty regarding the optimal drug regimens for medical management.²

Before the current NICE guideline CG154 (3) was published in 2012, common practice was to use a combination of mifepristone and misoprostol (MifeMiso combination). The 2012 NICE guideline, however, recommended that misoprostol alone should be given to women having medical management (3). This recommendation was based on very limited evidence from one study of 115 women (4), which found no difference between MifeMiso combination and misoprostol alone. Recognising the limited available evidence, the NICE guideline and HTA have called for a trial.

2.1.1 Existing evidence

We conducted a systematic review of trials investigating the use of mifepristone and misoprostol in women with miscarriage to gain a better understanding of studied interventions, outcomes and resolution rates. These studies are listed in Table 1. In addition to the publication by Stockheim et al., one more trial was identified (5), which compared MifeMiso combination versus misoprostol alone in the missed miscarriage population. Together, the two trials included a total of 242 patients treated with mifepristone and misoprostol or misoprostol alone. Meta-analysis of the results showed no significant difference between the two trial arms for outcome of resolution of miscarriage (risk ratio (RR) 0.97 95% confidence interval (CI): 0.82 to 1.13) (Figure 1). However, given the imprecision that inevitably accompanies such small sample sizes, it is not possible to draw any firm inferences.

Study	Intervention	Comparison	Risk of Bias
Gronlund 2002 <i>n</i> =127	600mg oral mifepristone and 400mcg misoprostol 48 hours later	400mcg vaginal misoprostol and 200mcg misoprostol two hours later if no vaginal bleeding occurred	Centres randomised to treatment regimens with crossover every 4 months; allocation concealment inadequate; No blinding of patients and study personnel.
Stockheim 2006 <i>n</i> =115	600mg oral mifepristone and 800mcg oral misoprostol 48 hours later	800mcg oral misoprostol and 800mcg oral misoprostol 48 hours later	Method of randomisation clear; no allocation concealment; No blinding of patients and study personnel.

Table 1. Randomised trials of MifeMiso combination versus misoprostol alone for the medical management of missed miscarriage.

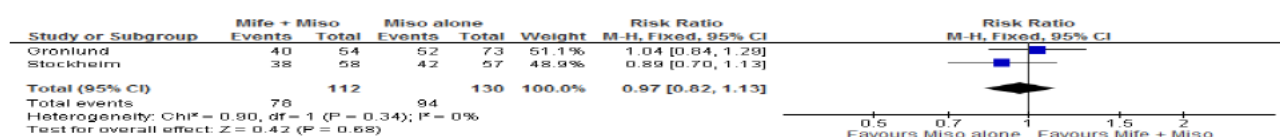


Figure 1. Forest plot of completed trials comparing MifeMiso combination versus misoprostol alone for the medical management of missed miscarriage, for the outcome of resolution of miscarriage.

2.1.2 Support for the MifeMiso trial

To understand how the existing evidence is viewed by clinicians, we conducted a national survey of clinicians. The findings are provided below.

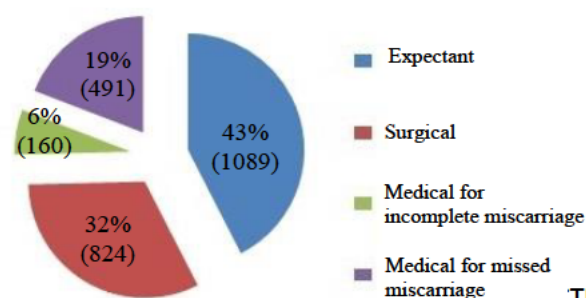


Figure 2. Unit survey of miscarriage treatment over a three month period (Aug-Oct 2015) at 14 hospitals.

Why are we only investigating the medical management of missed miscarriage?

We performed a survey of 14 hospital trusts over a 3 month period. We found 25% (651/2564) of all miscarriages were managed medically (Figure 2). Of the medically managed miscarriages, 75% (491/651) were

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for missed miscarriage, supporting our focus on the women with missed miscarriage, as opposed to those with incomplete miscarriage.

Furthermore, our survey found 79% (120/152) of health professionals from 82 NHS trusts believe that a trial is required to answer this question for missed miscarriage compared with only 38% (58/152) of health professionals for the question in women with incomplete miscarriage.

Data from 82 hospital trusts across the UK indicates that 82% (67/82) of healthcare providers offering medical management use misoprostol alone (Figure 3). The remaining 18% (15/82) use a combination of mifepristone and misoprostol despite the recommendations of NICE Guideline CG154.

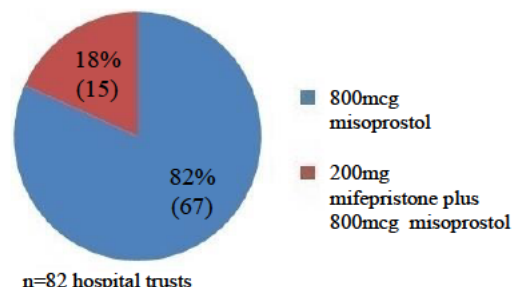


Figure 3. Current practice for the treatment of missed miscarriage.

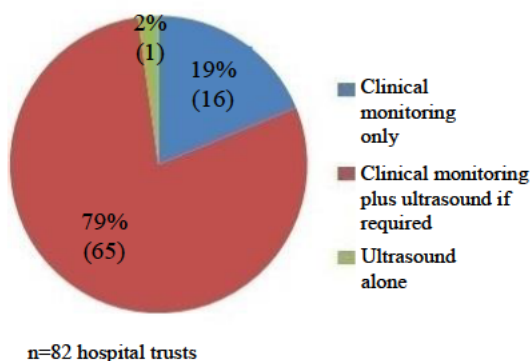


Figure 4. Current practice for assessing resolution of miscarriage.

How is resolution of miscarriage assessed?

Resolution of miscarriage in the majority of trusts (79%) is confirmed by clinical monitoring and ultrasound where required (Figure 4).

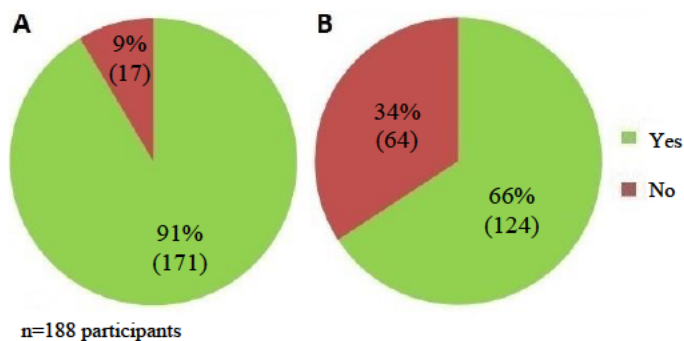


Figure 5. Patient opinion on (A) whether they think a trial is needed and (B) would they be willing to take part?

Are patients willing to take part?

We conducted a UK patient survey (n=188 women) in conjunction with the Miscarriage Association in Dec 2015. 91%

(171/188) of women thought the trial would be worthwhile, and 66% (124/188) stated they would agree to take part if offered the study (Figure 5). Most women surveyed considered that non-retention of pregnancy tissue is an outcome of primary importance. As above, this collective opinion has informed our selection of complete expulsion of the gestational sac from the uterus as the primary outcome measure for the trial.

WHY IS A TRIAL NEEDED NOW?

1. NICE guideline CG154 calls for a definitive trial to evaluate whether there is any benefit in using mifepristone in addition to misoprostol.
2. A patient survey supports the study. The survey (n=188) showed that 66% of women would consider taking part in the study (section 2.1.2 above).
3. A UK clinician survey supports the study. In the survey of 152 practitioners, 79% believed that a clinical trial is needed to investigate whether the mifepristone and misoprostol combination is more effective than misoprostol alone in the medical management of missed miscarriage.
4. The Association of Early Pregnancy Units, Early Pregnancy Clinical Studies Group, the Miscarriage Association and the Tommy's Charity support this research.
5. If benefit is confirmed in the MifeMiso trial, women and the NHS stand to gain substantially. On the other hand, if mifepristone is found to be ineffective, treatment with mifepristone can be avoided.
6. Mifepristone treatment is cheap (£17.55 per 200mg oral tablet), and if benefit is confirmed, we expect rapid uptake of this intervention.

2.1.3 Aims and objectives

Aim: To investigate the clinical and cost-effectiveness of MifeMiso combination (mifepristone and misoprostol) versus misoprostol alone in the management of missed miscarriage.

Primary clinical objective: To test the hypothesis that treatment with mifepristone plus misoprostol is superior to misoprostol alone for the resolution of miscarriage within 7 days in women diagnosed with missed miscarriage by pelvic ultrasound scan in the first 13+6 weeks of pregnancy.

Key secondary objective:

To test the hypothesis that the addition of mifepristone reduces the need for surgical intervention to resolve the miscarriage.

Other secondary objectives:

1. To evaluate if the addition of mifepristone reduces the need for further doses of misoprostol.
2. To evaluate if the addition of mifepristone improves other clinical outcomes including surgical intervention up to and including 7 days post-randomisation and after 7 days post-randomisation, duration of bleeding, infection, negative pregnancy test at 21 days post-randomisation, time from randomisation to discharge from EPU care, side effects and complications.
3. To evaluate if the addition of mifepristone improves patient satisfaction
4. To assess the cost-effectiveness of the combination of mifepristone and misoprostol in the medical management of missed miscarriage.

Economic objectives: To assess the cost-effectiveness of the combination of mifepristone and misoprostol in the medical management of missed miscarriage based on an outcome of additional cost per additional successfully managed miscarriage and additional cost per additional quality-adjusted life-year (QALY). Using a model-based economic evaluation we will further explore the cost-effectiveness of the medical management of missed miscarriage, as explored in the proposed trial, with alternative management strategies, such as surgical and expectant, based on available secondary sources.

Mixed-method evaluation objectives: To explore the satisfaction of patients who complete the trial protocol. The results of the satisfaction survey (CSQ-8) will act as a sampling frame to conduct semi-structured interviews to further investigate patient experiences and satisfaction with medical management of missed miscarriage.

3 Trial design

3.1 Design

A randomised, parallel group, double-blind, placebo-controlled multicentre study, with health economic and mixed-methods evaluation.

3.2 Source of potential participants

Potential participants will be identified and approached by clinic doctors, nurses, and research nurses/midwives in the Early Pregnancy Assessment Units (EPAUs) of participating centres. They will be clearly advised that participation in the study is entirely voluntary with the option of withdrawing from the study at any stage, and that participation or non-participation will not affect their usual care. Potential participants will be provided with a study Participant Information Sheet (PIS) and given time to consider their involvement. Women who give consent will proceed to randomisation if they are eligible to participate in the trial. Consent will be recorded on the approved consent form, which must be retained in the site file and medical notes, with a copy given to the participant and a copy sent to the MifeMiso Trial Office. Further consent will be obtained from those patients that are approached and agree to take part in the semi-structured mixed-methods interview.

3.3 Eligibility criteria

3.3.1 Inclusion criteria

- Women diagnosed with missed miscarriage by pelvic ultrasound scan in the first 13+6 weeks of pregnancy opting for medical management of miscarriage.
- Age 16 years and over.
- Willing and able to give informed consent.

3.3.2 Exclusion criteria

- Women opting for alternative methods of miscarriage management (expectant or surgical)
- Diagnosis of incomplete miscarriage.
- Life threatening bleeding.
- Contraindications to mifepristone or misoprostol use for example chronic adrenal failure, known hypersensitivity to either drug, haemorrhagic disorders and anticoagulant therapy, prosthetic heart

valve or history of endocarditis, existing cardiovascular disease, severe asthma uncontrolled by therapy or inherited porphyria.

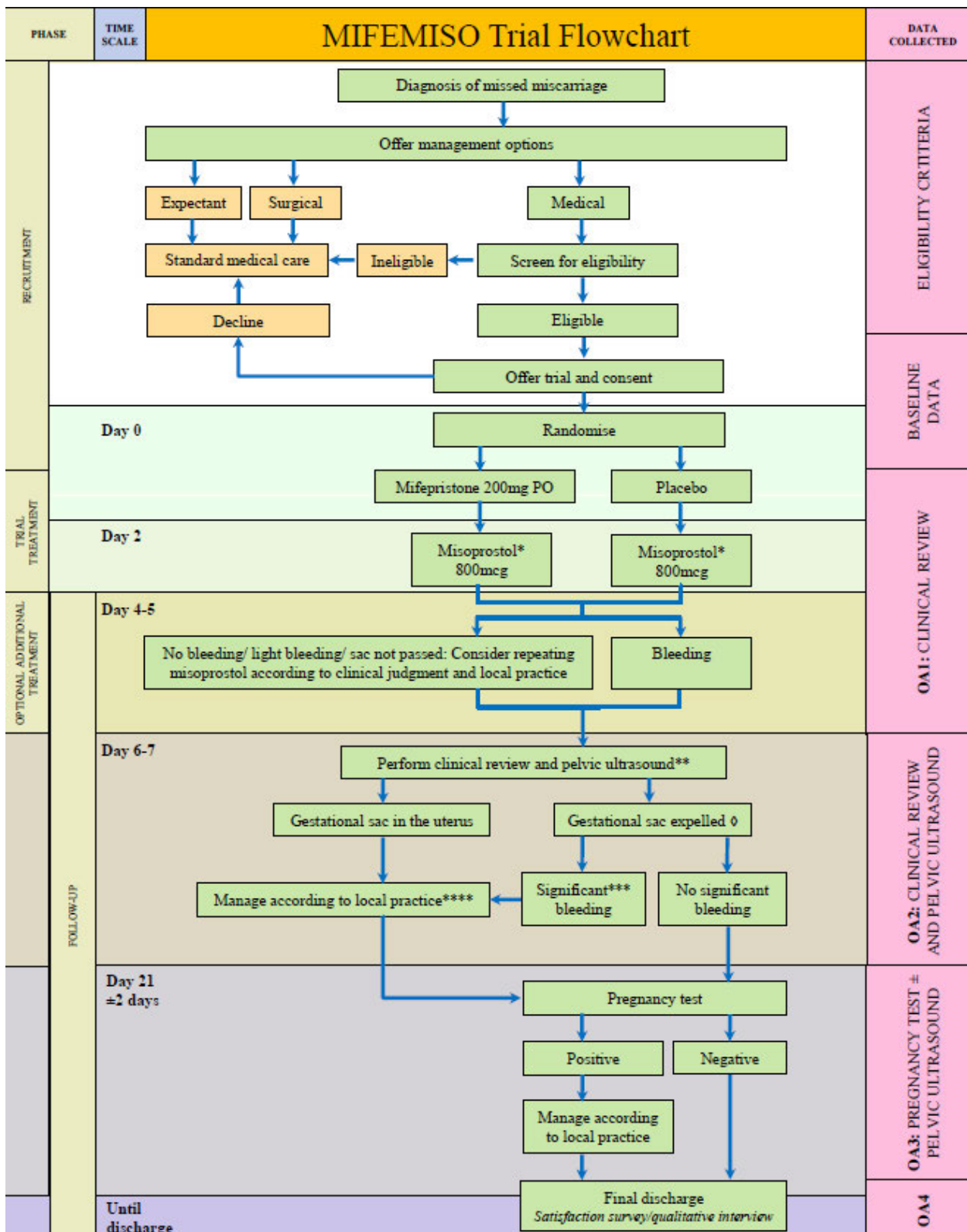
- Current participation in another blinded, placebo-controlled trial of investigational medicinal products in pregnancy.
- Previous participation in the MifeMiso trial
- Woman not able to attend for day 6-7 ultrasound scan

3.3.3 Ineligible and declining patients

All women who are identified with missed miscarriage and opt for medical management but are ineligible for the trial, or decline participation, should have the reasons for non-recruitment recorded on the screening log, along with their ethnic group, initials and year of birth. This information will describe the representativeness of the trial population.

Over the duration of study recruitment, it is feasible that a woman who has already participated in MifeMiso will have a subsequent missed miscarriage and will receive treatment at a participating centre. Previous participation in MifeMiso precludes enrolment of the same individual twice in the trial for any subsequent missed miscarriage.

3.4 Trial flowchart



◊ Primary outcome.
 * If gestational sac has been passed before the scheduled time for misoprostol, misoprostol can be omitted
 ** If scan performed earlier than day 6-7 and sac passed then repeat scan at day 6-7 not required
 *** According to clinical judgment
 **** Advice: Avoid surgical evacuation unless clinically indicated

Figure 6. MifeMiso trial flowchart

3.5 Consent

It will be the responsibility of the Investigator to obtain written informed consent for each participant prior to performing any trial related procedure. A research nurse, research midwife or clinician is able to take consent providing that local practice allows this and responsibility has been delegated by the Principal Investigator as captured on the Site Signature and Delegation Log.

A Participant Information Sheet (PIS) will be provided to facilitate this process. Investigators, or delegates, will ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the participant. They will also stress that participation is voluntary and that the participant is free to refuse to take part and may withdraw from the trial at any time. The participant will be given sufficient time to read the PIS and to discuss their participation with others outside of the site research team. The participant will be given the opportunity to ask questions. If the participant expresses an interest in participating in the trial they will be asked to sign and date the latest version of the Informed Consent Form (ICF). The participant must give explicit consent for the regulatory authorities, members of the research team and/or representatives of the sponsor to be given direct access to the participant's medical records.

The Investigator, or delegate, will then sign and date the form. A copy of the ICF will be given to the participant, a copy will be filed in the medical notes, and the original placed in the Investigator Site File (ISF). Once the participant is entered into the trial, the participant's trial number will be entered on the Informed Consent Form maintained in the ISF. In addition, if the participant has given explicit consent a copy of the signed Informed Consent Form will be sent to the BCTU trials team for review.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to participant and version number of ICF signed and date consent received. Where consent is obtained on the same day that the trial related assessments are due to start, a note should be made in the medical notes as to what time the patient was approached about taking part in the trial, the time consent was obtained and what time the procedures started.

At each visit the participant's willingness to continue in the trial will be ascertained and documented in the medical notes. Throughout the trial the participant will have the opportunity to ask questions about the trial. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

Electronic copies of the PIS and ICF will be available from the Trials Office and for UK trials will be printed or photocopied onto the headed paper of the local institution. Details of all participants approached about the trial will be recorded on the Participant Screening/Enrolment Log and with the participant's prior consent, their General Practitioner (GP) will also be informed that they are taking part in the trial.

3.6 Randomisation

3.6.1 The randomisation process

Immediately after all eligibility criteria have been confirmed, consent has been obtained and all baseline prognostic factors gathered, a woman will be randomised into the trial. Women will be randomised into the trial by a secure online randomisation system which is available via the MedSciNet Clinical Trial Framework (www.medscinet.net/mifemiso). Unique log-in usernames and passwords will be provided to those who are required to use the online system and/or who have been delegated the role of randomising participants into the study as detailed on the MifeMiso Trial Signature and Delegation Log. The online randomisation system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance. A telephone toll-free randomisation service (0800 953 0274) is available Monday to Friday, 09:00 to 17:00 UK time, except for bank holidays and University of Birmingham closed days.

Registration paperwork will be provided to investigators and may be used to collate the necessary information prior to randomisation. All the questions and data items on the registration paperwork must be answered before a trial number and pack number may be given. If some data items are missing, randomisation will be suspended but may be resumed once the information is available. Only when all the eligibility criteria and baseline data items have been provided, will the trial and treatment pack numbers be given and a confirmatory email sent to the randomising investigator, the local Principal Investigator, the research midwife/nurse, the local pharmacist and the MifeMiso trial office. The trial number will be linked to a treatment pack number that will be available in the local hospital pharmacy.

Investigators will keep their own study file log which links women with their allocated trial number in the MifeMiso Patient Recruitment and Identification Log. The Investigator must maintain this document, which is not for submission to the Trials Office. The Investigator will also maintain the MifeMiso Screening Log which is accessible through the MifeMiso online randomisation system. The MifeMiso Patient Recruitment and Identification Log and MifeMiso Participant Screening/Enrolment Log should be held in strict confidence.

3.6.2 Minimisation variables

Participants will be randomised online via a secure internet facility in a 1:1 ratio through an Integrated Trial Management System. A minimisation procedure using a computer-based algorithm will be used to avoid chance imbalances in important prognostic variables. Variables used in the minimisation will be:

- Maternal age (<30, ≥30 years).
- Body mass index (BMI) (<35, ≥35 kg/m²).
- Previous parity (nulliparous, parous women).
- Gestational age (<70, ≥70 days).
- Amount of bleeding (Pictorial Blood Assessment Chart score; ≤2, ≥3)
- Randomising centre.

A 'random element' will be included in the minimisation algorithm, so that each woman has a probability (unspecified here) of being randomised to the opposite treatment that they would have otherwise received.

3.6.3 Informing the participant's GP

The participant's General Practitioner (GP) will be notified, with the participant's consent.

4 Trial treatment

4.1 Investigational Medicinal Product: Mifepristone and placebo

The Investigational Medicinal Product (IMP) is a single dose of 200mg mifepristone to be taken orally after confirmation of missed miscarriage by pelvic ultrasound scan. The dose of 200mg is being used as it is the most commonly used dose for the medical management of miscarriage when used with misoprostol and it is the most commonly studied dose in published trials investigating its efficacy in the medical management of miscarriage. The approved Summary of Product Characteristics (SmPC) for mifepristone (17-Jun-2013) is available to all participating units, which will be used to form the Reference Safety Information (RSI).

The placebo will be an oral tablet in the same form as the IMP, and identical in appearance.

4.2 Packaging, Formulation and Supply

The trial medication is based on licensed and commercially available Mifegyne (Mifepristone) 200mg tablets. For purposes of blinding, placebo to match tablets will be developed and manufactured for the Mifegyne tablets. MODEPHARMA is responsible for arranging the active drug sourcing, placebo manufacturing and labelling/randomised packaging of all IMPs and final QP release for clinical trial use (according to Annex 13 guidelines). The labelled and QP released medication will be shipped to trial sites following site initiation.

Please refer to the Summary of Product Characteristics for Mifegyne 200mg tablets as well as the Investigational Medicinal Product Dossier (IMP Dossier) for more details about the active and placebo study drug products.

At study initiation, the Trial Office will arrange an initial supply of mifepristone and placebo to be delivered to the pharmacist of each study site. Local pharmacists will check the amount and condition of the supply, and confirm these details in a Proof of Receipt form.

The SmPC for Mifegyne states that there are no special storage precautions. The trial drug should be stored at 30°C or below. All the details of trial drug supply, labelling, storage and preparation will be as per the requirements of the Medicines for Human Use (Clinical Trials) Regulations 2004.

4.3 Dispensing and Accountability

At randomisation, the trial treatment number will be provided and this reference will correspond to a trial treatment pack available in the local hospital pharmacy. The pharmacist will receive notification of the name and trial number of the randomised woman and will prepare the trial treatment for dispensing.

The local pharmacist should keep accurate records of trial drugs dispensed using a pharmacy log provided by the MifeMiso Trial Office. Trial drugs must be kept in the packaging supplied and under no circumstances used for other participants or non-participants.

4.4 Resupply to Centres

The computer program underpinning the randomisation process will automatically notify MODEPHARMA Ltd when a local study centre supply is low, to enable the IMP provider to issue another batch of trial drugs to the pharmacy. However, if the local pharmacist notices that supplies are becoming depleted and additional supplies could be needed, the site should contact the MifeMiso Trial Office, who will be able to initiate an additional supply.

4.5 Compliance monitoring

The dispensing of the MifeMiso trial drug will be recorded in the pharmacy drug accountability log. Ingestion of the drug will be observed by a healthcare professional and documented in the patient's notes. Compliance to trial treatment will be defined as taking the allocated mifepristone/placebo on day 0 and subsequently misoprostol on day 2 unless the gestational sac has been passed before the scheduled time for misoprostol; in the latter case, the patient will be deemed to be compliant to the trial medication as long as the allocated mifepristone/placebo is taken on day 0.

4.6 Excluded medications or interactions

Anticoagulant therapy (low molecular weight heparin or warfarin) is known to interact with mifepristone. Therefore patients currently using these medications will not be recruited to the trial.

4.7 Withdrawal of treatment

A participant may be withdrawn from trial treatment if it becomes medically necessary in the opinion of the investigator(s) or clinician(s) providing patient care. In the event of such premature treatment cessation, MifeMiso study personnel will make every effort to obtain and record information about the reasons for discontinuation and any adverse events, and to follow up all safety and efficacy outcomes as appropriate.

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation.

Participants should be aware at the beginning that they can freely withdraw (discontinue participation) from the trial (or part of) at any time.

Types of withdrawal as defined are:

- The participant would like to withdraw from trial treatment, but is willing to be followed up in accordance with the schedule of assessments and if applicable using any central UK NHS bodies for long term outcomes (i.e. the participant has agreed that data can be collected and used in the trial analysis)
- The participant would like to withdraw from trial treatment and does not wish to attend trial visits in accordance with the schedule of assessments but is willing to be followed up at standard clinic visits and if applicable using any central UK NHS bodies for long term outcomes (i.e. the participant has agreed that data can be collected at standard clinic visits and used in the trial analysis, including data collected as part of long term outcomes)
- The participant would like to withdraw from trial treatment and is not willing to be followed up in any way for the purposes of the trial and for no further data to be collected (i.e. only data collected prior to the withdrawal can be used in the trial analysis)

or

- On rare occasion, the participant wishes to withdraw completely (i.e. from trial treatment and all follow up) and is not willing to have any of their data, including that already collected, to be used in any future trial analysis.

The details of withdrawal (date, reason and type of withdrawal) should be clearly documented in the source data.

4.8 Unblinding

Participants, investigators, research midwives/nurses and other attending clinicians will remain blind to the trial drug allocation throughout the duration of the trial however investigators will have access to unblinding in case of a medical emergency via the online code-break system or by contacting the MifeMiso Trial office.

Should any Serious Adverse Event occur, the management and care of the participant will be initiated as though the woman is taking mifepristone. Cases that are considered serious, unexpected and possibly, probably or definitely related (please refer to section 5.2) will be unblinded only at the Trial Office by the MifeMiso Trial Manager (or other nominated individual), for reporting purposes. Requests to unblind will be considered by the C.I. (or delegate) prior to a decision being made. The attending clinician and local PI will not be made aware of the actual trial drug.

In all other circumstances, investigators and research midwives/nurses will remain blind to drug allocation whilst the woman remains in the trial. However, if a woman is withdrawn from the treatment and only if the drug allocation is required for the continued medical management of the withdrawn participant, clinicians should contact the MifeMiso Trial Office or use the online MifeMiso code-break system. (In all cases, the P.I. should be involved in the decision to unblind a participant). This service will be available 24 hours a day, seven days a week and will facilitate rapid unblinding. If they wish, participants may enquire and find out about their drug allocation (mifepristone or placebo) after the trial has ended by contacting their local hospital or trial office directly.

5 Safety monitoring procedures

The Medicines for Human Use (Clinical Trials) Regulations 2004 define categories of adverse events, the responsibilities of the investigators to notify adverse events to the Trial Sponsor and the responsibilities of the Trial Sponsor to report to the regulatory authority and ethics committee.

5.1 Reporting period

Details of specific AEs with a severity grade of 3, 4, or 5 will be documented and reported from the date of commencement of protocol defined treatment until resolution of the miscarriage. SAEs that are judged to be at least possibly related to the IMP must still be reported in an expedited manner until resolution of the miscarriage.

5.2 Severity and causality categorisation

The assessment of severity of AEs and SAEs to the trial drug is a clinical decision based on all available information at the time. The following categories, as outlined in Table 2, will be used to define the severity of the AE/SAE.

Category	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activities of daily living (ADL)**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Table 2. Categorisation of severity for all events. * Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. ** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bed ridden.

The assessment of relationship of AEs and SAEs to the trial drug is a clinical decision based on all available information at the time. The following categories, as outlined in Table 3, will be used to define the causality of the AE/SAE.

Category	Definition
Definitely related	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably related	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly related	There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the patient's clinical condition, other concomitant events)
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). There is another reasonable explanation for the event (e.g., the patient's clinical condition, other concomitant treatments)
Unrelated	There is no evidence of any causal relationship

Table 3. Categorisation of causality for all events.

5.3 Adverse Events (AEs) and Adverse Reactions (ARs)

An AE is:

- Any unintentional, unfavourable clinical sign or symptom.
- Any new illness or disease or the deterioration of existing disease or illness.
- Any clinically significant deterioration in any laboratory assessments or clinical tests.

Certain AEs are commonly encountered in participants receiving mifepristone. As the safety profile of the IMP used in this trial is well characterised, it is highly unlikely that this trial will reveal any new safety information relating to this intervention. Therefore, only AEs that are graded with a severity grade of 3, 4 or 5 (refer to Table 2) that are experienced during treatment (regardless of the causality assessment) need to be reported.

An AR is an Adverse Event that is considered to be ‘possibly related’, ‘probably related’ or ‘definitely related’ to the trial drug (refer to Table 3).

5.3.1 Reporting AEs and ARs

Specific AEs with a severity grade of 3, 4, or 5, from the first administration of trial treatment until the resolution of the miscarriage, whether observed directly or reported by the participant, will be collected and recorded. It will not be necessary to report non-serious adverse reactions or events.

5.4 Serious Adverse Events (SAEs)

An SAE is an untoward event which:

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

All events which meet the definition of serious, with the exception of the hospital admission events described below, will be collected and recorded in the participant notes and the CRF. SAEs will in addition be reported to the trials office immediately and within 24 hours of being made aware of the event.

A Serious Adverse Reaction (SAR) is a Serious Adverse Event that is considered to have a “reasonable causal relationship” with the trial drug.

**Life-threatening in the definition of a Serious Adverse Event or Serious Adverse Reaction 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. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.*

Events NOT considered to be SAEs are hospitalisations for the expected events listed below. These events will be recorded on the electronic Case Report Form (e-CRF) and reported to the DMC and MifeMiso trial office as part of the safety review. They include any of the following:

- a) Hospital admission with vaginal bleeding
- b) Hospital admission with abdominal pain

- c) Hospital admission for surgical management of miscarriage
- d) Hospital admission for a condition unrelated to miscarriage management

These events would not require expedited (immediate) reporting by the site and would not be regarded as unexpected for the purpose of this trial, unless they are reported with an increased frequency or result in an unexpected outcome. An AE form will be completed for these events.

5.4.1 Reporting SAEs

Investigators will report all AEs that meet the definition of an SAE immediately and within 24 hours of being made aware of the event. All SAEs must be recorded on the SAE Form (a sample document is available separately) and submitted to the Trial Office via fax (0121 415 9136) or email (to bwh-tr.mifemiso@nhs.net). The investigator will assess severity and causality of each SAE.

For each SAE, the following information will be collected:

- Full details in medical terms with a diagnosis, if possible.
- Duration (start and end dates; times, if applicable).
- Action taken.
- Outcome.
- Severity, in the opinion of the investigator.
- Causality, in the opinion of the investigator.

Assessment of causality and severity must be made by a doctor. If a doctor is unavailable, initial reports without causality and severity assessment must be submitted to the Trial Office by a healthcare professional within 24 hours, and followed up by medical assessment as soon as possible thereafter, ideally within the following 24 hours. All events considered at site to be 'possibly related', 'probably related' or 'definitely related' will be reported by the trial office as related. All events considered at site to be 'unlikely' or 'not related' will be reported by the trial office as unrelated.

Where an SAE form has been completed by someone other than the Investigator, the original SAE form will be required to be countersigned by the Investigator to confirm agreement with the causality and severity assessments.

The local investigator and others responsible for patient care should institute any supplementary investigations of SAEs based on their clinical judgement of the likely causative factors. They should also provide further follow-up information as soon as available. If a participant dies, the causative factors identified in any post-mortem findings must be provided to the Trial Office.

Any SAE that is outstanding at the end of the trial treatment period must be followed up at least until the final outcome is determined, even if this provision necessitates continued follow-up beyond the resolution of the miscarriage.

On receipt of an SAE form, the BCTU trials team will allocate each SAE a unique reference number in the trial database and return this via email to the site as proof of receipt. If the site has not received confirmation of receipt of the SAE from the BCTU or if the SAE has not been assigned a unique SAE identification number, the site should contact the BCTU trials team within 1 working day. The site and the BCTU trials team should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the Site File.

On receipt of an SAE form the CI, or delegate, will independently determine the severity and causality of the SAE. Expected SAEs are those listed in the approved version of the SmPC for mifepristone (which acts as the RSI). These events do not meet the criteria for classification as Suspected Unexpected Serious Adverse Reactions (SUSARs) unless for reason of their severity. A copy of the approved RSI will be made available to all participating units and the Trial Office will ensure that any updates are circulated to all investigators.

An SAE judged by the CI (or delegate) to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The causality assessment given by the investigator will not be downgraded by the CI (or delegate). If the CI (or delegate) disagrees with the Principal Investigator's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

All SARs should be categorised as expected or unexpected by the CI with reference to the RSI (see table 4). Expected SARs are those listed in the RSI contained within the Summary of Product Characteristics (SmPC) for Mifegyne 200mg tablets. These events do not meet the criteria of a SUSAR unless for reason of their severity/frequency or outcome.

Category	Definition
Expected	An adverse reaction that is classed in nature as serious and which is consistent with the information about the IMP listed in the RSI
Unexpected	An adverse reaction that is classed in nature as serious and which is inconsistent with the information about the IMP listed in the RSI

Table 4. Definition of expectedness for SARs.

The Trial Office will report all SAEs/SARs to the DMC and TSC approximately yearly. The DMC will view data blinded to treatment but will be able to review unblinded data if necessary. The Trial Office will also report all SAEs/SARs to the Research Ethics Committee (REC), Medicines and Healthcare Products Regulatory Agency (MHRA) and sponsor annually in the form of a Development Safety Update Report (DSUR). The REC, MHRA and TSC will only view data blinded to trial treatment. Local investigators will be responsible for reporting SAEs to their host institutions, according to local regulations. The MHRA, REC and sponsor will be notified immediately if a significant safety issue is identified during the course of the trial.

5.5 Suspected Unexpected Serious Adverse Reactions (SUSARs)

A SUSAR is a Suspected Unexpected Serious Adverse Reaction, the nature or severity of which are not consistent with the RSI for mifepristone contained within the approved version of the SmPC.

5.5.1 Reporting SUSARs

Any SAE that is categorised as both (a) suspected to be related to the MifeMiso trial drug and (b) unexpected will be classified as a SUSAR, and subject to expedited reporting, irrespective of trial arm (mifepristone or placebo).

All SUSARs will be recorded on the SAE Form. The Chief Investigator (CI) or nominated individual will undertake an urgent review of SUSARs within 24 hours of reporting and may request further information immediately from the local clinical team. The CI will not overrule the severity or causality assessment of the

local investigator. If the CI disagrees with the assessment of the local investigator, further clarification and discussion should take place to reach a consensus. If a consensus cannot be reached, both the opinion of the local investigator and the CI should be provided in reports to the REC and MHRA.

The Trial Office will report all SUSARs to the Sponsor, REC and MHRA. The treatment allocation will be unblinded. If any SUSAR results in death or is life-threatening then the report will be made within 7 days of the initial report being received. Detailed follow-up information will be provided within an additional 8 days. All other events categorised as SUSARs will be reported within 15 days.

If information is incomplete at the time of initial reporting, or the event is ongoing, the Trial Office will request follow-up information, including information for categorisation of causality, from the local investigator, and send the follow-up information to the Sponsor, REC and MHRA within an additional 8 days for fatal or life-threatening SUSARs and as soon as possible for any other events.

5.6 Notification of Deaths

All deaths will be reported to the Trial Office on the SAE Form irrespective of whether the death is related to the trial drug or an unrelated event. If a participant dies, any post-mortem findings must be provided to the Trial Office with the SAE form. The Trial Office will report all deaths to the DMC for continuous safety review.

6 Pharmacovigilance

6.1 Local Principal Investigator (PI) (or nominated individual)

- To sign an Investigator's Agreement accepting the responsibilities below:
- To record specified AE/ARs occurring in the trial participants.
- To report all serious, expected or unexpected adverse events or reactions, in the appropriate timescale.
- To provide medical judgement in assigning severity and causality to AEs.
- To fax or email SAE forms to the Trial Office within 24 hours of becoming aware, and to provide further follow-up information as soon as available.
- To report SAEs to local committees if required, in line with local arrangements.

6.2 Chief Investigator (CI) (or nominated individual)

- To review causality and make expectedness assessment of SAEs
- To review all events assessed as SAEs in the opinion of the local investigator.
- To review all events assessed as SUSARs in the opinion of the local investigator.

6.3 MifeMiso Trial Office

- To report SUSARs, unblinded to treatment, to the REC and MHRA within required timelines as detailed above.
- To prepare annual safety reports, blinded to treatment, to the REC, MHRA and sponsor
- To prepare SAE safety reports for the DMC at approximately six-monthly intervals (data will be presented blinded to treatment, but the DMC will be able to review unblinded data if necessary).
- To report all fatal SAEs to the DMC for continuous safety review.
- To notify investigators of SUSARs which compromise participant safety.

6.4 Trial Steering Committee (TSC)

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

6.5 Data Monitoring Committee (DMC)

- To review (initially at intervals of at least twelve months) overall safety and morbidity data to identify safety issues that may not be apparent on a case-by-case basis.
- To recommend to the TSC whether the trial should continue unchanged, continue with protocol modifications, or stop.

7 Follow-up and outcome measures

7.1 Primary outcome

- Failure to spontaneously pass the gestational sac within 7 days after randomisation. This will be assessed by pelvic ultrasonography where possible.

7.2 Key secondary outcome

- Surgical intervention to resolve the miscarriage (collected up to discharge from EPU care)

7.3 Other secondary outcomes

- Surgical intervention to resolve the miscarriage up to and including day 7 post-randomisation
- Surgical intervention to resolve the miscarriage after day 7 post-randomisation to discharge from EPU care
- Need for further doses of misoprostol up to day 7 post-randomisation
- Need for further doses of misoprostol up to discharge from EPU care
- Overall patient satisfaction score (measured using the CSQ-8 questionnaire and collected upon discharge from EPU care).
- Patient quality of life (index value and overall health status measured using the EQ-5D-5L questionnaire and collected on date of randomisation, day 6-7 post-randomisation or day of follow-up USS if different to day 6-7 and day 21 +/- 2 days post-randomisation. If a woman obtains an initial positive pregnancy test result at day 21 +/- 2 days post-randomisation then a further EQ-5D-5L questionnaire is collected upon discharge from EPU care).
- Duration of bleeding reported by woman (days) (collected up to discharge from EPU care)
- Diagnosis of infection associated with miscarriage requiring outpatient antibiotic treatment (collected up to discharge from EPU care)
- Diagnosis of infection associated with miscarriage requiring inpatient antibiotic treatment (collected up to discharge from EPU care)
- Negative pregnancy test result 21 days (\pm 2 days) after randomisation.
- Time from randomisation to discharge from EPU care (described using summary statistics only)

7.4 Safety outcomes

- Blood transfusion required (collected up to discharge from EPU care)
- Side effects (collected up to discharge from EPU care)
- Death (collected up to discharge from EPU care)
- Any serious complications (collected up to discharge from EPU care)

7.5 Health economic evaluation

If the combination of mifepristone and misoprostol (MifeMiso) results in a complete and safe resolution of miscarriage with more women being successfully managed relative to misoprostol alone, significant economic implications may be seen for the health sector. For example, MifeMiso may result in fewer miscarriage surgeries and blood transfusions as well as fewer inpatient stays and better psychological health compared with misoprostol alone. However, the additional cost of including mifepristone would need to be justified and shown to provide good value for the public health care resources, which could be more effectively spent elsewhere in the health system. An economic evaluation is, therefore, required to assess the cost-effectiveness of MifeMiso in the management of missed miscarriage.

Economic data collection: Resource use data will be collected prospectively, through case report forms, in order to estimate the overall cost of drug administration, management of miscarriage, and follow-up care until discharge from EPU care) associated with the two arms of the trial. The main resource categories related to miscarriage that will be monitored include:

- Drug administration
- Resource use associated with adverse events and complications, such as blood transfusion and infection
- Resource use associated with outpatient or emergency visits and hospital admissions until final discharge, for example if a miscarriage surgery is needed

In order to estimate the overall cost of each trial-arm, unit costs will be applied to each resource item. Information on unit costs will be obtained from key UK national sources, such as the NHS reference costs (8), the Unit Costs of Health and Social Care (6), the British National Formulary (7), and the Office for National Statistics.

Given the potential impact of miscarriage on physical and, particularly, psychological health (8), health-related quality of life data will be obtained based on participants responses to the EQ-5D-5L at baseline and at each relevant clinical review. A preference-based index of health-related quality of life will be derived using the recently published English value set (9), and Quality-Adjusted Life-Years (QALYs) will be calculated using the area under the curve approach.

Economic analysis: A trial-based economic evaluation will initially explore the cost-effectiveness of MifeMiso in the medical management of missed miscarriage compared with the use of misoprostol alone. A model-based economic evaluation will additionally be undertaken to assess the cost-effectiveness of the medical management of missed miscarriage, as explored in the proposed trial, with alternative management strategies, such as surgical and expectant, based on available secondary sources.

Trial-based economic evaluation: The economic analysis will be initially framed in terms of cost-consequences, reporting data in a disaggregated manner on the incremental cost and important outcomes

as assessed in the trial. An incremental cost-effectiveness analysis will be carried out based on the outcomes of cost per successfully managed miscarriage and cost per QALY at final discharge. The main analysis will adopt the NHS perspective. Other secondary clinical outcomes will also be explored in the economic evaluation. If preliminary results show that the clinical outcomes are likely to generate cost differences between arms in the Personal Social Service (PSS) or productivity components, then an attempt will be made to explore the PSS and societal perspectives in secondary analyses using evidence from the literature if available.

Multiple imputation with chained equations will be used to avoid loss of efficiency and potential bias of results with the exclusion of participants with missing economic data, although a complete-case analysis will also be carried out and reported for completeness. To account for the skewed distribution commonly seen in economic data and the uncertainty around cost-effectiveness point-estimates, bootstrap methods will be used.

Model-based economic evaluation: Decision modelling is required to synthesize the available evidence on the management of missed miscarriage and account for the inherent uncertainty in order to offer a more comprehensive basis for decision makers on the relative cost-effectiveness of the medical management of missed miscarriage, as proposed in the trial, compared with alternative management strategies. For this analysis, a decision tree will be used given the short-term nature of the decision problem. To parameterize the model, we will utilise the clinical evidence gathered in the systematic review conducted from our co-investigators as part of this proposal. To supplement the clinical evidence, a systematic review of cost-effectiveness studies will be carried out in line with the UK Centre for Reviews and Dissemination guidelines (10), and the following databases will be searched: MEDLINE (Ovid), EMBASE (Ovid), Cochrane Library (Wiley), NHS EED, and CINAHL (Ebsco). Similar to the trial-based economic evaluation, unit cost estimates will be drawn from standard national sources, and an incremental cost-effectiveness analysis will be undertaken based on the outcomes of cost per successfully managed miscarriage and cost per QALY from both the NHS perspective if data are available.

The results of these economic analyses will be presented using cost-effectiveness acceptability frontiers to reflect decision uncertainty across different thresholds of willingness-to-pay per additional unit of outcome. Deterministic and probabilistic sensitivity analyses will be undertaken to explore the robustness of the findings to plausible variations in key assumptions and analytical methods used, and to consider the broader issue of generalisability of the study's results.

7.6 Mixed-methods evaluation

We will undertake a patient satisfaction survey with all participants recruited using a validated eight item client satisfaction questionnaire (CSQ-8) (11). The CSQ-8 is a widely used instrument for assessing client satisfaction with health and human services, and has been used in previous trials of treatment for miscarriage (see (12) for example). The CSQ-8 is a brief, standardized measure of client satisfaction that is comprised of eight items. Each item asks respondents to provide their opinion and conclusions about services they have received. Each question is scored out of four, with total scores ranging from 8-32 points, with higher scores indicating higher levels of satisfaction. The CSQ-8 will be administered in paper and electronic format (via SmartSurvey). The results from this survey will be used as a sampling frame via which we will purposively sample those participants who were satisfied/found the service acceptable, and those who did not, for a semi-structured interview. The interview guide will be developed based on existing literature (see for example: 13, 14, 15), patient and public involvement, and discussions within the research

team. A maximum variation sample (total n=50 in two interview groups: (a) 20-25 of those who report being satisfied/ found the service acceptable, and (b) 20-25 with those who report that they were dissatisfied/ found the service unacceptable) of trial participants will be purposively identified and recruited to ensure that we can explore a broad range of views and experiences of participation. Within each interview group, the purposive sample will include women according to trial site, age, body mass index, gestational age and parity. From experience, we expect the final sample to include approximately 50 interviews but the numbers will remain flexible to ensure that we collect sufficiently rich data to answer the research questions. Women who agree to take part in an interview will be offered the choice as to whether the interview takes place in their own home, a private room at the University of Birmingham (if local to Birmingham), via telephone or via video call software e.g. Skype, and will be consented prior to the interview data collection. We will aim to conduct interviews within six weeks of completion of the trial protocol. Interviews will be audio recorded, with data collection and analysis running in parallel, and the framework method (16) will be used to facilitate a systematic and flexible approach to the analysis.

7.7 Outcomes for future studies

Each participant in the MifeMiso study will be asked to consent for the future evaluation of themselves and any subsequent pregnancies using the health records of both. Although long-term follow-up will remain outside the scope of this trial, we plan to conduct further studies on outcomes such as subsequent successful pregnancies post-miscarriage resolution.

7.8 Outcome assessment

7.8.1 Format and frequency

Relevant trial data will be transcribed directly into the web-based database. Source data will comprise the research clinic notes, hospital notes and ultrasound scan results.

Women will be encouraged to report adverse events and any additional visits to non-participating hospitals to their local research team. Self-reports will be verified against clinical notes by the research team.

The outcome assessments for the study are detailed in Table 5.

Outcome assessed	When?	How?	By whom?	Protocol driven (PD) or Standard Practice (SP)
Baseline data: EQ-5D-5L questionnaire	Day 0	Face to face clinical appointment with participant	Self-administered questionnaire	PD
OA1: Clinical review	Day 4-5	Telephonic or face to face clinical appointment with participant	Local research nurse/midwife or doctor	SP and PD
OA2: Clinical review +/- pelvic ultrasound, to determine whether the gestation sac has been expelled.	Day 6-7	Face to face clinical appointment with participant	Local research nurse/midwife or doctor	PD (and SP in some hospitals depending on trust policy)
OA2: EQ-5D-5L questionnaire	Day 6-7	Face to face clinical appointment with	Self-administered questionnaire	PD

		participant		
OA3: Pregnancy test	Day 21± 2 days (point of discharge for women with negative pregnancy test result)	Clinical records and/or telephonic interview or face to face clinical appointment with participant	Local research nurse/midwife or doctor	SP
OA3: EQ-5D-5L questionnaire	Day 21± 2 days (point of discharge for women with negative pregnancy test result)	Telephonic or face to face clinical appointment with participant	Self-administered questionnaire	PD
OA4: Final discharge	Upon discharge	From clinical records or interview with the participant	Local research nurse/midwife or doctor	SP
OA4: EQ-5D-5L questionnaire (if initial positive pregnancy test result) and patient satisfaction survey	Upon discharge	Telephonic or face to face clinical appointment with participant	Self-administered questionnaires	PD
OA4: Semi-structured qualitative interview	Within 6 weeks of discharge	Face to face, via telephone or via video call with participant	Qualitative/mixed- methods researcher	PD

Table 5. Outcome assessment details

7.9 Data management and validation

7.9.1 Source data

In order to allow for the accurate reconstruction of the trial and clinical management of the subject, source data will be accessible and maintained. The vast majority of source data will be kept at site in the participant's medical notes. Exceptions to this include the EQ-5D-5L questionnaire completed at 21 days post-randomisation and subsequently upon discharge (for women who obtain an initial positive pregnancy test result), the patient satisfaction survey completed at discharge, and the transcript of the in-depth qualitative interview (see section 7.7.3 for further details). These data will be stored at the MifeMiso trial office.

7.9.2 CRF completion

e-CRFs will be completed by research staff in the MedSciNet Clinical Trial Framework. Patient questionnaires that are sent to the MifeMiso trial office will be entered onto the database by staff in the BCTU research team in accordance with the trial specific work instructions. Data reported on each form will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Staff delegated to complete CRFs will be trained to adhere to CRF completion guidelines. In all cases it remains the responsibility of the site's Principal Investigator to ensure that the CRF has been completed correctly and that the data are accurate. Where applicable for the trial this will be evidenced by the signature of the site's Principal Investigator on the CRF.

7.9.3 Participant completed questionnaires

Participant completed EQ-5D-5L questionnaires will be administered and completed by the participant at baseline and at each relevant clinical review. The patient satisfaction survey will be completed at the time of discharge from hospital care. Participant completed questionnaire training will be overseen by the research team at site, who can answer any questions the participant may have regarding the rationale and method of assessment. The participant will be asked to complete the questionnaires during the clinic visit (prior to other clinical assessments) or at home where required. Ideally the questionnaire should be completed by the participant alone (without assistance from friends, family or the clinical or research team). Any assistance or proxy completion should be recorded and flagged to the trials office. For forms completed during the clinic visit, the participant completed questionnaires will be checked on site by a member of the research team for missing data. The participant will be given the opportunity to complete any missing data. For forms completed at home, the patient will be provided with a pre-paid, self-addressed envelope which will be used to send the completed questionnaires to the MifeMiso trial office. Alternatively women may return completed forms to the MifeMiso NHS.net email account or, for the CSQ-8, women may complete this electronically via SmartSurvey.

Staff delegated to administer Participant completed questionnaires will be trained to adhere to the following Participant completed questionnaire completion guidelines:

- Participant completed questionnaires to be completed in accordance with completion instructions.
- Participants will be encouraged to answer all questions when completing the participant completed questionnaires.
- Participant completed questionnaires will be checked for missing data and where feasible participants will be given the opportunity to complete any missing data.

7.9.4 Loss to follow-up

To reduce loss to follow-up, the local research team will record the NHS numbers of participants, to trace the participants via local GP practices and non-participating NHS trusts where necessary.

7.9.5 Withdrawal of Consent for Further Data Collection

Withdrawal from follow-up will be the decision of each participant in the MifeMiso study (please refer to section 4.7). However, the exclusion of withdrawn participants in data analysis could bias clinical trial results and reduce the power of the study to detect important differences, therefore women will be encouraged to allow data collection to continue even if trial treatment ceases.

7.10 End of Trial Definition

The interventional phase of the trial will end when the last woman recruited has taken her last dose of the trial treatment. The observational phase of the trial to assess clinical outcomes will cease when the final outcome of the woman has been completed and data has been entered onto the database and validated as being ready for analysis. The last woman interviewed from the subset of women selected for interview up to 6 weeks after discharge will be used to define the end of trial. The Trials Office will notify the MHRA, REC and sponsor that the trial has ended within 90 days of the end of trial. Where the trial has terminated early, the Trials Office will inform the MHRA, REC and sponsor within 15 days of the end of trial. The Trials Office will provide them with a summary of the clinical trial report within 12 months of the end of trial.

7.11 Blinded Endpoint Review Committee

A Blinded Endpoint Review Committee (BERC) will assess participant data relevant to the primary outcome for women who have not received an ultrasound scan within 7 days post-randomisation (or have received a scan but scan results regarding passage of the gestational sac are not recorded), . The BERC will assess whether sufficient additional information is available for the participant data to be included in the derivation of the primary outcome.

The BERC will meet following the end of recruitment to MifeMiso. The review will be undertaken blinded to treatment allocation. Only cases where the Committee unanimously decide that there is sufficient additional information available to derive the primary outcome will be included in the primary analysis of the primary outcome.

Data recorded by the site research team in the electronic case report forms (e-CRFs) and self-report information obtained by the National Clinical Coordinator from contacting the woman directly will be made available for the BERC to review. This information will be made available to Committee members on the day of their meeting(s) via an electronic Primary Outcome Review Form held on the trial database, along with the relevant e-CRF data. Paper copies of relevant e-CRFs and file notes detailing self-report information from women will also be provided. The Trial manager will minute Committee discussions and enter a summary of the discussions along with the decision as to whether a participant case can be included in the derivation of the primary outcome data on to the electronic version of the Primary Outcome Review form on the trial database.

Members of the Committee are required to formally register their assent to join the Committee by signing a separate charter. Further details of the BERC can be found in this charter.

8 Recruitment and analysis

8.1 Sample size

We plan to randomise 710 women, 355 participants in each group. 670 women will need to be evaluated to detect a Minimally Important Difference (MID) of 10% reduction in the rate of failure to spontaneously pass the gestational sac within 7 days (i.e. from 25% to 15%), assuming 90% power and a type I error rate of 5%. However, assuming and adjusting for a worst case scenario of 5% attrition, the total number of participants required will be 710. The 25% [95% CI: 23% to 27%] control group estimate is taken from our systematic review (unpublished data) and the 10% MID was the most popular selection from our health professional survey (41% of those surveyed). The estimate of the control group rate will be monitored throughout the recruitment period by the independent DMC to ascertain if any deviations from this assumption will impact on the sample size calculation.

8.2 Projected Accrual and Attrition Rates

Participants will be recruited from participating centres across the UK. Approximately 32 hospital units in the UK will contribute to the total, with more sites joining the study if required to randomise 710 women within two years.

8.3 Statistical analyses

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of these analyses is given below. The primary comparison groups will be composed of those treated with mifepristone and misoprostol versus those treated with placebo and misoprostol. In the first instance, all analyses will be based on the intention to treat principle, i.e. all participants will be analysed in the treatment group to which they were randomised irrespective of compliance or other protocol violation. For all outcome measures summary statistics and treatment effect measures will be presented with 95% confidence intervals. Effect measures will be adjusted for the minimisation variables listed in section 3.6.2 where possible. P-values will be presented for the primary and key secondary outcomes, allowing for multiple comparisons following a hierarchical testing procedure. That is to say, the null hypothesis for the primary outcome will be tested first (at the 5% significance level) and if and only if the test is statistically significant will the key secondary outcome be tested. Otherwise, no further hypothesis testing will be performed. P-values will be presented for all safety outcomes unadjusted for multiple testing. Results from all other secondary outcomes will be treated as exploratory rather than confirmatory. No adjustments for multiple testing will be made for confidence intervals.

8.3.1 Primary outcome analysis

The primary endpoint will be the proportion of women randomised who failed to spontaneously pass the gestational sac within 7 days after randomisation (mifepristone or placebo). The denominator of this proportion will be all women randomised in the specific treatment group, and the numerator will be those women in the corresponding group that failed to spontaneously pass the gestational sac within 7 days after randomisation. We will use a log-binomial regression model to calculate the adjusted risk ratio and 95% confidence intervals. If this fails to converge alternative models will be used (e.g. Poisson regression). The p-value from the associated model will be produced and used to determine statistical significance at the 5% level.

8.3.2 Secondary outcome analyses

Appropriate summary statistics split by randomised group will be presented for each outcome (e.g. proportions/percentages, mean/standard deviation or median/interquartile range). The key secondary outcome will be analysed as for the primary outcome, with the associated p-value only presented if the primary outcome reaches statistical significance at the 5% level (see section 8.3.1). All other dichotomous secondary outcomes (e.g. need for further doses of misoprostol, need for surgery) will be analysed in the same fashion but no p-values will be presented. Continuous outcomes (such as days of bleeding) will be analysed with the use of a linear mixed regression model and adjusted mean differences will be presented with associated 95% confidence intervals. All safety outcomes will be analysed as for the primary outcome with associated 95% confidence intervals and p-values presented. The number of participants with serious adverse events per group will be analysed with a chi-squared test.

8.3.3 Handling Missing Data

Every attempt will be made to collect full follow-up data on all women (unless a woman withdraws consent for follow up data collection). In particular, participants will continue to be followed up even after any protocol treatment deviation or violation. It is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis. This presents a

risk of bias, and a sensitivity analysis will be undertaken to assess the possible impact of the risk, (e.g. using methods based on multiple imputation).

The derivation of the primary outcome is based on information regarding passage of the gestational sac by USS at 6-7 days post randomisation, or self-report data reviewed by a Blinded End-point Review Committee if USS information is not available. A sensitivity analysis will be undertaken restricted to participants with available USS information only, to assess the robustness of the results that include clinical criteria for the primary outcome derivation.

8.3.4 Subgroup Analyses

Subgroup analyses will be limited to the primary outcome (including those adjudicated by the BERC) and the same variables used as minimisation variables (please refer to section 3.6.2; excluding centre). The subgroup defined by gestational age (<70, ≥70 days) is of special interest; analyses of other subgroups will be presented for exploratory purposes and interpreted cautiously. Tests for statistical heterogeneity (e.g. by including treatment group by subgroup interaction parameter in the regression model) will be performed prior to any examination of effect estimate within subgroups. The results of subgroup analyses will be treated with caution, and used for the purposes of hypothesis generation only.

8.3.5 Interim Analyses

Interim analyses of safety and efficacy for presentation to the independent DMC will take place during the study. The committee will meet prior to study commencement to agree the manner and timing of such analyses but this is likely to include the analysis of the primary and major secondary outcomes and full assessment of safety (serious adverse events) at least at annual intervals. Criteria for stopping or modifying the study based on this information will be ratified by the DMC. Details of the agreed plan will be written into the Statistical Analysis Plan. Further details of DMC arrangements are given in section 9.6.

8.3.6 Final Analysis

The primary analysis for the study will occur after all randomised women have complete primary and major secondary outcomes (approximately 21 days after treatment commencement) and data has been entered onto the database and validated as being ready for analysis.

9 Data access and quality assurance

9.1 Confidentiality of Personal Data

Personal data and sensitive information required for the MifeMiso trial will be collected directly from trial participants and hospital notes. Participants will be informed about the transfer of this information to the MifeMiso Trial Office and asked for their consent. The data will be entered onto a secure computer database, directly via the internet using secure socket layer encryption technology or indirectly from paper forms by members of the research team.

Any trial-related personal information received in paper format or interview audio files and verbatim transcripts will be held securely and treated as strictly confidential according to the Standard Operating Procedure (SOP) of the Birmingham Clinical Trials Unit (BCTU). All the staff involved in the MifeMiso trial

(clinical, academic and support personnel) will share the same duty of care to prevent any unauthorised disclosure of personal information. No data that could be used to identify an individual will be published. Data will be stored on a secure server under the provisions of the Data Protection Act and/or applicable laws and regulations.

All studies at the University of Birmingham have to be registered with the Data Protection officer and data held in accordance with the data protection act. The University will designate a Data Protection Officer upon registration of the study. The Study Centre has arrangements in place for the secure storage and processing of the study data which comply with the University of Birmingham policies. The University of Birmingham has Data Protection Registration to cover the purposes of analysis and for the classes of data requested. The University's Data Protection Registration number is Z6195856.

9.2 Data management

Processes will be employed to facilitate the accuracy of the data included in the final report. These processes will be detailed in the trial specific data management plan. Coding and validation will be agreed between the trial team and the trial programmer and the trial database will be signed off once the implementation of these has been assured. The data management plan will detail the process for dealing with data queries which will be managed through the use of data clarification forms. The type of self-evident corrections that can be made will be agreed.

9.3 In-house data quality assurance

Members of the MifeMiso trial management team will perform hospital site monitoring visits where necessary as part of the trial monitoring plan, as agreed and reviewed by the TMG. This may involve source data verification.

9.3.1 Site set-up and initiation

The CI will be required to sign an internal CI agreement with the sponsor which will also list the responsibilities delegated from the sponsor to the CI. A separate agreement between the CI and BCTU will be completed, which includes a task delegation log between the CI and the BCTU. Both these agreement documents must be completed prior to trial commencement. All participating investigators will be asked to sign the necessary agreements. All members of the site research team will also be required to sign the Site Signature and Delegation Log. Prior to commencing recruitment all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, Adverse Event reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File and Pharmacy File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The BCTU trials team must be informed immediately of any change in the site research team.

9.3.2 Monitoring and audit

Monitoring will be carried out as required following a risk assessment and as documented in the monitoring plan. Investigators and their host institutions will be required to permit trial-related monitoring and audits by the MifeMiso Trial Manager and/or a member of the trial monitoring team providing direct access to source data and documents as requested. Additional on-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of participant withdrawals or deviations. If a monitoring visit is required the Trials team will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the

MifeMiso trial staff access to source documents as requested. NHS Trusts may also be subject to inspection by the MHRA and/or internal Research and Development Managers, and should do everything requested by the CI in order to prepare and contribute to any inspection or audit. Study participants will be made aware by the PIS of the possibility of external audits of the data they provide.

9.3.3 Central monitoring throughout the trial

The trial will also adopt a centralised approach to monitoring data quality and compliance. Within the MedSciNet Clinical Trial Framework, a computer database will be constructed and tailored specifically to the MifeMiso trial, with range and logic checks to prevent erroneous data entry. Independent checks of data entry will be periodically undertaken on small subsamples. The Trial Statistician will regularly check the balance of allocations by the minimisation variables.

9.4 Notification of Serious Breaches

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial, within 7 days of becoming aware of that breach.

For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree the safety or physical or mental integrity of the subjects of the trial; or the scientific value of the trial. Sites are therefore requested to notify the Trials office of any suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trials Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action. Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the Trial Management Group, Trial Steering Committee, the REC and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the REC and MHRA. A copy is sent to the University of Birmingham Clinical Research Compliance Team at the time of reporting to the REC and/or relevant regulatory bodies.

9.5 Independent Trial Steering Committee (TSC)

The TSC will provide independent supervision for the trial, providing advice to the CI and co-investigators and the trial Sponsor, and affording protection for participants by ensuring the study is conducted according to the International Conference on Harmonisation (ICH) of Good Clinical Practice (GCP) guidelines.

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

9.6 Data Monitoring Committee (DMC)

The DMC will adopt the DAMOCLES charter to define its terms of reference and operation in relation to oversight of the MifeMiso trial. If mifepristone is overwhelmingly better or worse than placebo with respect

to reducing passage of the gestational sac by 7 days, then this effect may become apparent before the target recruitment has been reached. Alternatively, new evidence could emerge from other sources to suggest that mifepristone is definitely more, or less, effective than placebo. To protect against any unnecessary continuance of the trial in this event, interim analyses of major endpoints will be supplied during the period of recruitment to the study, in strict confidence, to the DMC along with updates on results of other related studies, and any other analyses that the DMC may request.

The DMC will advise the chair of the TSC if, in their view, any of the randomised comparisons in the trial have provided both (a) proof beyond reasonable doubt that for all, or for some, types of participant one particular treatment is definitely indicated or definitely contra-indicated in terms of a net difference in the primary outcome, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results. Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least $p < 0.001$ (similar to a Haybittle-Peto stopping boundary) in an interim analysis of the primary outcome may be required to justify halting, or modifying, the study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed. The TSC will then be able to decide whether to close or modify any part of the trial. Unless this happens, however, the TMG, TSC, the investigators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results.

9.7 Archiving

On completion of data collection and in accordance with the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (sections 18 and 28), It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source documents (e.g. signed Informed Consent Forms, Investigator Site Files, Pharmacy Files, participants' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 25 years. This will allow adequate time for review and reappraisal, to enable the resolution of any queries or concerns about the results, and to facilitate further follow-up research.

After the closure of the trial, the site files from each centre will be securely archived at the sites. Electronic trial data will be securely stored within the MedSciNet Clinical Trial Framework. The remainder of the trial master file documentation will be securely stored by the MifeMiso Trial Office at the University of Birmingham. Long-term legacy archiving for electronic data will be considered for continued storage after 25 years.

9.8 Data Sharing

Anonymous data will be made available to other researchers, for example for individual participant data meta-analysis, if the aim is to answer further unresolved questions in a scientifically rigorous study design, following review by the TMG or CI or nominated data custodian.

10 Organisation and responsibilities

To ensure the smooth running of the trial and to minimise the overall procedural workload, each participating centre will designate appropriately trained and qualified local individuals to be responsible for the institutional coordination of clinical and administrative arrangements.

All MifeMiso investigators will be responsible for (a) maintaining the protocol of the trial as described in this document, (b) helping healthcare professionals to ensure the study participants receive appropriate care throughout the period of research enrolment, (c) protecting the integrity and confidentiality of clinical and other records and data that may be generated by the research, and (d) reporting any failures in these respects, adverse drug reactions and other events or suspected misconduct through the appropriate systems.

As part of the BCTU, which is a fully registered UK Clinical Research Collaboration clinical trials unit, the MifeMiso Trial Office will benefit from accumulated experience in the management of studies with a focus on Women's Health and pregnancy. The BCTU will provide a robust quality management system to ensure good practice in the conduct and statistical analysis of the project.

10.1 Centre Eligibility

Participating centres will be NHS hospitals, with at least one of the following:

- Dedicated EPAU where suspected miscarriages are managed.
- Gynaecology ward.

Each study centre must use an onsite pharmacy to dispense medications to participants, and be able to offer appointments for the women in a dedicated clinical setting.

10.2 Local coordinators

10.2.1 Local Principal Investigators

Every study centre will nominate a local Principal Investigator (PI) to oversee the conduct of MifeMiso research at the particular institution. Every PI must sign a declaration to acknowledge these responsibilities. It will be important to ensure close collaboration between clinical teams, in order to identify eligible participants sufficiently early for entry. The responsibilities of local PIs will include ensuring that all medical, nursing and midwifery staff who may be involved in the care of miscarriages and infertility services remain well-informed about the study and trained in trial procedures, such as obtaining informed consent and other aspects of GCP. The local PIs will also liaise with the Trial Manager to manage the logistic and administrative arrangements of the trial.

10.2.2 Nursing or Midwifery Coordinators

Each participating centre should also designate a local nurse or midwife to ensure that all eligible patients are considered for the study, provided with a PIS, and offered an opportunity to discuss the study if required. This person may be responsible for collecting baseline data, assessing eligibility, performing randomisation and coordinating follow-up evaluations. They will receive updates and newsletters from the Trial Office, provided with appropriate training and invited to progress meetings.

10.2.3 The MifeMiso Trial Office

The MifeMiso Trial Office will be responsible for providing study materials such as folders with printed and promotional literature, and for supplying these documents to collaborating centres after any relevant ethical approvals are obtained. The Trial Office will also supply additional printed materials on request, provide a central randomisation service, and take responsibility for data collection and verification (including reports of SAEs thought to be due to trial treatment), to notify SUSARs to the Trial Sponsor

and/or regulatory authorities and for analyses. The Trial Office will additionally help resolve any local problems that may be encountered in trial participation.

10.2.4 Research Governance

The trial will be conducted according to the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments, and the principles of GCP guidelines.

Investigators at all the participating centres will be required to sign an Investigator's Agreement to confirm their commitments to accrual, compliance, GCP, confidentiality and publication. Deviations from the Investigator's Agreement will be monitored and the TSC will decide whether any action needs to be taken, e.g. withdrawal of funding or the suspension of study activities at the site.

The Trial Office will ensure that any researchers not employed by an NHS organisation who may be in a position to influence the care of participants, or require access to participant notes, obtain a research passport or letter of access.

10.2.5 Regulatory and Ethical Approvals

Ethical and Trust Management Approval

A favourable ethical opinion was granted from West Midlands - Edgbaston Research Ethics Committee (REC reference number 17/WM/0017).

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: <http://www.wma.net/en/30publications/10policies/b3/index.html>).

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments, the current Data Protection Act and the International Conference on Harmonisation Guidelines for Good Clinical Practice (ICH GCP). This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations. The protocol will be submitted to and approved by the main Research Ethics Committee (REC) prior to circulation.

Before any participants are enrolled into the trial, the Principal Investigator at each site is required to obtain local R&D approval/assurance. Sites will not be permitted to enrol participants until written confirmation of R&D approval/assurance is received by the BCTU trials team.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

Clinical Trial Authorisation

The Trial Office has obtained a unique EudraCT number for the trial (2016-005097-35), and has Clinical Trials Authorisation (CTA) from the MHRA.

10.3 Funding and finance

The research costs of the MifeMiso trial are funded by a grant from the NIHR Health Technology Assessment (HTA) programme awarded to the University of Birmingham.

10.4 Indemnity

There are no special arrangements for compensation for non-negligent harm suffered by participants as a result of participating in the study. The study will not be sponsored by industry and therefore the indemnity guidelines of the Association of the British Pharmaceutical Industry (ABPI) and Association of British Healthcare Industries (ABHI) will not apply. The standard NHS indemnity liability arrangements for research detailed in Health and Safety Guidance (HSG) 96 (48) will operate in this case.

However, it should be stressed that in terms of negligent liability, NHS Trusts will retain a duty of care to all their patients, whether or not the patients are participating in a clinical trial. Apart from defective products, legal liability will not arise where there is non-negligent harm. NHS Trusts may not offer advance indemnities, nor take out commercial insurance for non-negligent harm.

10.5 Publication

A meeting will be held after the end of the study to allow discussion of the main results among the collaborators prior to publication. The success of the study will depend entirely on the wholehearted collaboration of a large number of doctors, nurses/midwives and others across the country. For this reason, the chief credit for the main results will be given not only to the central supervisory committees and/or organisers, but to all those who have collaborated in the trial.

10.6 Ancillary studies

Any proposals for formal additional studies of the effects of trial treatments on some participants (e.g. special investigations in selected hospitals) will be referred to the TMG for consideration. In general, it will be preferable for the trial to be kept as simple as possible, and add-on studies will need to be fully justified.

11 Dissemination and projected outputs

The impact of the trial question is intrinsically high, as confirmed by commissioned call for this research from the HTA. However, we have also prioritised methods to maximise impact from an early stage in the study design.

Guidelines: The information is expected to be rapidly incorporated into professional guidelines by the Association of Early Pregnancy Units (AEPU), the RCOG and NICE, and disseminated to Early Pregnancy Units nationally for implementation.

Patient information resources: The findings will inform lay resources, e.g. via patient organisations such as the Miscarriage Association and the Ectopic Pregnancy Trust. Lay information will also highlight the need

for treatment, if found beneficial, to be medically prescribed and supervised. Any negative findings will be equally disseminated to patients and the public to avoid unnecessary or potentially harmful intervention.

Conferences: The findings will be presented and disseminated via national and international conferences of AEPU and other relevant organisations.

Peer reviewed publications: We will aim to publish the findings in prestigious peer reviewed journals with a high impact factor. We will disseminate the completed papers to the Department of Health, the Scientific Advisory Committees of the RCOG, the Royal College of Nurses (RCN) and the AEPU.

NIHR Journals Library: If funded, the NIHR Journals Library will help to disseminate the findings and provide an important, permanent and comprehensive record of the study.

Media: In consultation with the investigators and appropriate journal representatives, a press release will be issued to the media upon publication of the results.

We will share the results of the study with trial participants, staff members at research sites and other related research groups in the area. We will also submit a formal notification to the REC, MHRA and the Department of Health. We anticipate additional outreach to other stakeholders (trial networks, healthcare advocates).

The trial team includes individuals with considerable previous experience of optimising research dissemination, including the Chairs of the RCOG Early Pregnancy Clinical Study Group (CSG) and AEPU, and the Director of the Miscarriage Association.

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