MifeMiso

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

Appendix VI: Statistical Analysis Plan

[redacted]

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

The MifeMiso Trial

Trial registration number: ISCRCTN 17405024

Statistical Analysis Plan

SAP Version Number	Protocol Version Number
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Statistical Analysis Plan (SAP) Amendments

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Abbreviations & Definitions	
Abbreviation / Acronym	**Meaning**
BCTU	Birmingham Clinical Trials Unit
BERC	Blinded Endpoint Review Committee
CONSORT	Consolidated Standards of Reporting Trials
DMC	Data Monitoring Committee
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention to Treat
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee
Term	**Definition**
International Standard Randomised Controlled Trial Number	A clinical trial registry
Protocol	Document that details the rationale, objectives, design, methodology and statistical considerations of the study
Randomisation	The process of assigning trial subjects to intervention or control groups using an element of chance to determine the assignments in order to reduce bias.
Statistical Analysis Plan	Pre-specified statistical methodology documented for the trial, either in the protocol or in a separate document.

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1. Introduction

This document gives a detailed statistical analysis plan (SAP) for the MifeMiso trial and should be read in conjunction with the current trial protocol. This SAP details the proposed analyses and presentation of the data for the main paper reporting the results for the MifeMiso trial.The results reported in these papers will follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (e.g. to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (e.g. transformation of data prior to analysis), but they are intended to establish rules that will be followed, as closely as possible, when analysing and reporting data.

Any deviations from this SAP will be described and justified in the final report or publication of the trial (using a table as shown in Appendix A). The analysis will be carried out by an appropriately qualified statistician, who should ensure integrity of the data during their data cleaning processes.

2. Background and rationale

The background and rationale for the trial are outlined in detail in the protocol. In brief, miscarriage is common (20% of pregnancies; approximately 125,000 miscarriages per year in England).[1] It is associated with not only physical harm, such as excessive bleeding, infection, and uterine perforation during surgery, but also substantial psychological impact on women. Miscarriage is estimated to cost the NHS £81 million per year.[2] 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. However, there is uncertainty regarding the optimal drug regimens for medical management.[3]

Before the current NICE guideline CG154[2] 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[2]. 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. In addition, the necessity of conducting such a trial was also supported by an unpublished patient survey (171/188 women thought worthwhile) and a clinician survey (120/152 of health professionals believe that a trial is necessary) at UK national level.

3. Trial objectives

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 women 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.

4. Trial methods

4.1. Trial design

MifeMiso is a randomised, parallel group, double-blind, placebo-controlled multicentre study, with health economic and mixed-methods evaluation (see Appendix B for trial schema).

Potential participants will be recruited from Early Pregnancy Assessment Units (EPAUs) of participating centres.

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 will be randomised to mifepristone plus misoprostol (MifeMiso combination) or misoprostol alone.

It is anticipated that the trial will last for three years. Women will be followed up until final discharge which is usually after 21±2 days since randomisation. A semi-structured qualitative interview will be conducted on a subset of participants within 6 weeks of discharge.

4.2. Trial interventions

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.

The 800mcg dose of misoprostol is justified by NICE guidance CG154.

4.3. Primary outcome measure

The primary outcome is failure to spontaneously pass the gestational sac within 7 days after randomisation. This will be assessed by pelvic ultrasonography where possible.

Some women will pass their gestational sac within 7 days post-randomisation and not attend hospital for pelvic ultrasonography at all or within 7 days. 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.

See Section 9.4 on data manipulations for how the primary outcome will be derived.

4.4. Secondary outcome measures

Secondary outcomes are as follows:

Key secondary outcome

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

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 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 (± 2 days) after randomisation
- Time from randomisation to discharge from EPU care (described using summary statistics only)

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)

The analysis of the patient quality of life secondary outcome will be undertaken as part of the health economic analysis, and for which the analysis method is documented separately.

4.5. Timing of outcome assessments

The schedule of trial procedures and outcome assessments are given in Appendix C.

4.6. Randomisation

Randomisation will be performed on-line on a 1:1 ratio via a secure internet facility through a third party independent Integrated Trial Management System (MedSciNet Clinical Trial Framework). A "minimisation" procedure using a computer-based algorithm will be used to avoid chance imbalances in the following important variables:

- Maternal age (<30, ≥30 years);
- Body mass index (<35, ≥35 kg/m^2);
- 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.

4.7. 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.

4.8. Framework

The objective of the trial is to test the superiority of one intervention to another.

The null hypothesis is that there is no difference in failure to spontaneously pass the gestational sac within 7 days after randomisation between the intervention groups. The alternative hypothesis is that there is a difference between the groups.

4.9. Interim analyses and stopping guidance

A separate Data Monitoring Committee (DMC) reporting template will be drafted and agreed by the DMC including an agreement on which outcomes will be reported at interim analyses. The statistical methods stated in this SAP will be followed for the outcomes included in the DMC report, where possible.

Interim analyses of safety and efficacy for presentation to the independent DMC will take place during the study. The committee met once prior to the study commencement to agree the manner and timing of such analyses which will include the analysis of the primary and major secondary outcomes and full assessment of safety (serious adverse events). Criteria for stopping or modifying the study based on this information have been ratified by the DMC.

4.10. Pilot Progression Rules

Not Applicable

4.11. Timing of final analysis

The final analysis for the trial will occur once the last randomised woman is discharged following the resolution of miscarriage and the corresponding outcome data has been entered onto the trial database and validated as being ready for analysis. This is provided that the trial has not been stopped early for any reason (e.g. DMC advice or funding body request).

4.12. Timing of other analyses

Not applicable.

4.13. Trial comparisons

All references in this document to 'group' refer to mifepristone plus misoprostol (MifeMiso combination) or placebo plus misoprostol (misoprostol alone).

5. Statistical Principles

5.1. Confidence intervals and p-values

Estimates of treatment effects for all outcomes will be presented with 95% confidence intervals. Two-tailed p-values will be presented for the primary, key secondary and safety outcomes according to the strategy set out in section 5.2.

5.2. Adjustments for multiplicity

Multiple comparisons will be allowed for by 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. In order to assess any signal within specific organ groups, P-values will be presented for all safety outcomes unadjusted for multiple testing, as type I error rates (false positives) are less of a concern. 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.

5.3. Analysis populations

All primary analyses (primary and secondary outcomes including safety outcomes) will be by intention-to-treat. Women will be analysed in the treatment group to which they were randomised, and all women shall be included whether or not they received the allocated treatment. This is to avoid any potential bias in the analysis.

5.4. Definition of adherence

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. This information will be collected on the trial specific data collection forms.

Adherence to allocated 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 adherent to the trial medication as long as the allocated mifepristone/placebo is taken on day 0.

5.5. Handing protocol deviations

A protocol deviation is defined as a failure to adhere to the protocol such as errors in applying the inclusion/exclusion criteria, the incorrect intervention being given, incorrect data being

collected or measured, follow-up visits outside the visit window or missed follow-up visits. We will apply a strict definition of the intention-to-treat-principle and will consider all randomised women as per the ITT population described in section 5.3 in the analysis, in some form, regardless of deviation from the protocol. [5] This includes women who were randomised but later found to violate the inclusion or exclusion criteria. It does not include those women who have specifically requested to withdraw consent for the use of their data in the first instance; however these outcomes will be explored as per other missing responses.

5.6. Unblinding

The unblinding of the Trial Statistician to the intervention code will take place once the database is locked for final analysis, unless the DMC request that they review the interim data with knowledge of the intervention groups or the DMC request to be unblinded at an interim analysis.

6. Trial population

6.1. Recruitment

A flow diagram (recommended by CONSORT[6]) will be produced to describe the patient flow through each stage of the trial. This will include information on the number (with reasons) of losses to follow-up (drop-outs and withdrawals) over the course of the trial. A template for reporting is given in Appendix D1.

6.2. Baseline characteristics

Categorical data will be summarised by frequencies and percentages. Continuous data will be summarised by the number of participants, mean and standard deviation if deemed to be normally distributed, median and interquartile range if data appear skewed, and ranges if appropriate. Tests of statistical significance will not be undertaken, nor confidence intervals presented.[7]

The trial population will be tabulated as per Appendix D2. The following minimisation, demographic and other baseline variables will be described for the total population and for the two randomised groups separately: maternal age (years), BMI (kg/m^2), previous parity, gestational age (days), amount of bleeding, ethnicity, medical history (current medication, diabetes, renal disease, cardiac disease, chronic hypertension, thyroid disease, cancer, other), and number of previous pregnancies (live birth, stillbirth, miscarriage, ectopic pregnancy, molar pregnancy, termination, pregnancy of unknown location).

7. Intervention(s)

7.1. Description of the interventions

A template for reporting information on the intervention(s) is given in Appendix D3.

7.2. Adherence to allocated intervention

A cross-tabulation of allocated treatment by the adherence categories stated in section 5.4 will be produced (proportions and percentages). A template for reporting adherence is given in Appendix D4.

8. Protocol deviations

Frequencies and percentages by group will be tabulated for the protocol deviations as per Appendix D5.

9. Analysis methods

Intervention groups will be compared using generalised estimating equations, or a similar method, to adjust for all covariates as specified in section 9.1, where possible.

9.1. Covariate adjustment

In the first instance, all estimates of treatment effects between groups for all outcomes will be adjusted for the minimisation variables as listed in Section 4.6, where maternal age, body mass index and gestational age will be treated as continuous fixed effects, parity and bleeding score as categorical fixed effects, and randomising centre will be included as a random effect.

If covariate adjustment is not possible (e.g. the model does not converge), centre will be dropped from the model in the first instance. If convergence of the model remains problematic, alternative models will be explored (e.g. Poisson regression). If this fails, unadjusted estimates will be produced, and it will be made clear in the final report why this occurred (e.g. not possible due to low event rate/lack of model convergence).

9.2. Distributional assumptions and outlying responses

Distributional assumptions (e.g. normality of regression residuals for continuous outcomes) will be assessed visually (via histograms for any continuous data) prior to analysis; although in the first instance the proposed primary method of estimation stated in this analysis plan will be followed. If responses are considered to be particularly skewed and/or distributional assumptions violated and potentially affecting the analysis then this will be examined through sensitivity analysis consisting of transformations or bootstrapping techniques. In the case of skewed distributions of continuous responses, this will consist of transformation of responses prior to analysis (log transformation in the first instance, although others may be used if deemed appropriate). If extreme values are apparent and considered to be affecting the integrity of the analysis, a sensitivity analysis consisting of removing the outlying response(s) and repeating the analysis will be performed. Output from these analyses, if performed, will be described and presented alongside the primary analysis with the excluded values clearly labelled. See section 9.10 for further details regarding sensitivity analyses.

9.3. Handling missing data

Every attempt will be made to collect full follow-up data on all study women and so it is anticipated that missing data will be minimal. Women with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken on the primary outcome measure[8] to assess the possible impact of the risk and to make sure we are complying with the intention-to-treat principle.

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.

See section 9.10 for further details regarding sensitivity analyses.

9.4. Data manipulations

The Trial Statistician will derive all responses from the raw data recorded in the database as follows:

Outcome measures

- **Failure to spontaneously pass the gestational sac within 7 days after randomisation**

Reported on PART E (treatment allocation) on the Randomisation Form and Section C (ultrasound scan) and Section E (surgical intervention) on the Outcomes Form by answering the following questions:

a) Date of randomisation?
b) Did the woman undergo scan(s) post-randomisation?
c) If yes, was the sac passed?
d) When was the date of scan?
e) Did the woman require surgical intervention to resolve their miscarriage?
f) When was the date of surgery?

The date of randomisation and date of scan will be used to calculate the number of days at which the scan was performed after randomisation. If the sac was passed as confirmed by an ultrasound scan, and it was passed within 7 days since randomisation and no surgical intervention was used to resolve the miscarriage before day 7 since randomisation, then the primary outcome will be coded as NO (i.e. not failed). If surgery for removing the sac was carried out within 7 days since randomisation, or the sac was not yet passed following the last scan which was performed at day 6-7 or beyond since randomisation then the primary outcome will be coded as YES (failed). If a woman did not undergo any scan after

randomisation and there was no surgery performed before day 7 since randomisation, or the last scan was undertaken within 5 days after randomisation and the sac was still present the primary outcome will be coded as MISSING, unless cases where the BERC unanimously decide that there is sufficient information available to confirm whether or not the primary outcome has been achieved and whether the sac was passed or not spontaneously by day 7 post-randomisation. The following questions from the Primary Outcome Review Form will be used to determine this:-

A. Does the Committee unanimously agree that there is sufficient information available to confirm the primary outcome has been achieved?
B. Does the Committee unanimously agree whether the sac was passed or not spontaneously by day 7 post-randomisation?
C. Was the sac passed spontaneously by day 7 post-randomisation?
D. Does the Committee unanimously agree on the date sac passed?
E. Date sac passed

If A, B, C and D are all yes and E is before the date of surgery if surgery was required, then the primary outcome is NO (not failed).
If A and B are Yes and C is No, then the primary outcome is YES (failed).
If either A or B are No then C is not answered and the primary outcome remains MISSING.

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

Reported on Section E (Surgical intervention) on the Outcomes form by answering the question "Did the woman require surgical intervention to resolve their miscarriage?" where the date of surgery is on or before the EPU discharge date.

- **Surgical intervention to resolve the miscarriage up to and including day 7 post-randomisation**

Reported on Section E (Surgical intervention) on the Outcomes form by answering the question "Did the woman require surgical intervention to resolve their miscarriage?" where the date of surgery is ≤ 7 days after the randomisation date.

- **Surgical intervention to resolve the miscarriage after day 7 post-randomisation to discharge from EPU care**

Reported on Section E (Surgical intervention) on the Outcomes form by answering the question "Did the woman require surgical intervention to resolve their miscarriage?" where the date of surgery is >7 days after the randomisation date.

- **Need for further doses of misoprostol up to day 7 post-randomisation**

Reported on Section B (misoprostol administration) on the Outcomes Form by answering the question "Was misoprostol taken by the woman?" and if yes, "Date taken". Any further doses of misoprostol within 7 days since randomisation will be identified by calculating the time difference:

Date of misoprostol taken - Date of randomisation.

At least one of the time differences calculated above should fall within the range of 2 to 6 days inclusive and should not be the first dose to warrant a YES to the outcome measure.

- **Need for further doses of misoprostol up to discharge from EPU care**

Reported on Section B (misoprostol administration) on the Outcomes Form by answering the question "Was misoprostol taken by the woman?" and if yes, "Date taken" Any further doses of misoprostol throughout the trial will be identified by calculating the time difference:

Date of misoprostol taken - Date of randomisation.

At least one of the time differences calculated above should be greater than or equal to 2, should be taken on or before the date of discharge from EPU care, and should not be the first dose to warrant a YES to the outcome measure.

- **Overall patient satisfaction score (measured using CSQ-8 questionnaire and collected upon discharge from EPU care)**

The outcome will be defined using a validated eight item client satisfaction questionnaire (CSQ-8)[9]. 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[10]. 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. The overall score is produced by summing all item responses, with total scores ranging from 8-32 points, with higher scores indicating higher levels of satisfaction.

- **Duration of bleeding reported by woman (days) (collected up to discharge from EPU care)**

Reported on Section F (clinical outcomes until discharge) on the Outcomes form by answering "Date woman reported that bleeding started" and "Date woman reported that bleeding stopped", where days of bleeding will be computed from:

Date woman reported that bleeding stopped - Date woman reported that bleeding started.

This outcome will be treated as continuous.

- **Diagnosis of infection associated with miscarriage requiring outpatient antibiotic treatment (collected up to discharge from EPU care)**

Reported on Section F (clinical outcomes until discharge) on the Outcomes form by answering YES consecutively to the following three questions:

a) Was the woman diagnosed with an infection that was associated with miscarriage?
b) Were they treated as an outpatient?
c) Was the woman prescribed antibiotics for the infection?

A binary outcome will be defined based on whether or not the above three conditions were satisfied simultaneously. If any are missing then the outcome will be coded as MISSING.

- **Diagnosis of infection associated with miscarriage requiring inpatient antibiotic treatment (collected up to discharge from EPU care)**

Reported on Section F (clinical outcomes until discharge) on the Outcomes Form by answering YES consecutively to the following three questions:

a) Was the woman diagnosed with an infection that was associated with miscarriage?
b) Were they treated as an inpatient?
c) Was the woman prescribed antibiotics for the infection?

A binary outcome will be defined based on whether or not the above three conditions were satisfied simultaneously. If any are missing then the outcome will be coded as MISSING.

- **Negative pregnancy test result 21 days (± 2 days) after randomisation**

Reported on Section D (pregnancy test result) on the Outcomes form by answering YES to the question "Did the woman provide a pregnancy test result?" with a negative test result. A binary outcome will be defined based on whether the test result is positive or negative and a missing value will be taken if either the woman did not provide a pregnancy test result or the result is missing.

- **Time from randomisation to discharge from EPU care (described using summary statistics only)**

Reported on Section F (clinical outcomes until discharge) on the Outcomes form by answering the question "Date of final discharge from EPU care following a negative pregnancy test", and by calculating:
Date of final discharge from EPU care following a negative pregnancy test - Date of randomisation.

- **Blood transfusion required (collected up to discharge from EPU care)**

Reported on Section F (clinical outcomes until discharge) on the Outcomes form by answering the question "Did the woman require a blood transfusion from randomisation up until discharge from EPU care?" A binary variable will be defined. If a woman withdrew or was lost to follow up before being discharged, the binary outcome will take missing values.

- **Side effects (collected up to discharge from EPU care)**

Reported on the AE form AEs that are specified with a severity grade of 3, 4, or 5, from the first administration of trial treatment until discharge from EPU care. Events will be reported based on CTCAE category[12].
A binary outcome will be derived if a woman has at least one AE.

- **Death (collected up to discharge from EPU care)**

Reported on the SAE form.

- **Any serious complications (collected up to discharge from EPU care)**

Reported on the SAE form from the first administration of trial treatment until discharge from EPU care.

A binary outcome will be derived if a woman has at least one SAE.

9.5. Analysis methods – primary outcome(s)

- **Failure to spontaneously pass the gestational sac within 7 days after randomisation**

The primary outcome will be summarised using number of responses with percentages.
For the analysis of the primary outcome measure, a log-binomial regression model will be used to calculate the adjusted relative risk and 95% confidence intervals, after accounting for the possible clustering effect of randomising centres by using robust standard errors at centre level. The risk ratio will be adjusted for minimisation variables as detailed in section 9.1. The p-value from the associated model will be produced and used to assess statistical significance.

If the log-binomial model fails to converge, centre will be dropped from the model in the first instance. If convergence of the model remains problematic, it may be resolved by using Poisson regression with robust standard errors.[13] In the current case, the robust standard errors will be applied at centre level to account for the clustering effect of randomising centres. If this also fails to converge, unadjusted estimates will be produced from the log-binomial model. It will be made clear in the final report why this occurred (e.g. not possible due to low event rate/lack of model convergence).

In the primary analysis, participants with missing data for any reason will be excluded. Sensitivity analyses (see Section 9.10 below) will be undertaken using the same modelling approach.

A template for reporting the primary outcome is given in Appendix D6.

9.6. Analysis methods – secondary outcomes

Analyses for the binary secondary outcomes will be performed as per the primary outcome for the following outcome measures

- **Surgical intervention to resolve the miscarriage (collected up to discharge from EPU care)**
- **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**
- **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 (± 2 days) after randomisation**
- **Blood transfusion required (collected up to discharge from EPU care)**
- **Side effects (AEs collected up to discharge from EPU care)**
- **Death (collected up to discharge from EPU care)**
- **Any serious complications (SAEs collected up to discharge from EPU care)**

95% confidence intervals (and p-values for the key secondary outcome and safety outcomes) from the associated models will be presented according to the strategy detailed in section 5.2. No sensitivity analyses for these secondary outcome measures will be performed.

A template for reporting these binary secondary outcomes is given in Appendix D7.1 and D9.1.

Linear regression modelling will be used to compare

- **Overall patient satisfaction score (measured using the CSQ-8 questionnaire and collected upon discharge from EPU care).**
- **Duration of bleeding reported by woman (days) (collected up to discharge from EPU care)**

between the two treatment groups. The models will be adjusted for the minimisation variables as detailed in section 9.1 with the clustering effect of randomising centres accounted for by using robust standard errors at centre level. If the linear model fails to converge, centre will be dropped from the model in the first instance. If convergence of the model remains problematic, unadjusted estimates will be produced from the linear model. The adjusted mean differences between treatment groups will be presented along with the 95% confidence intervals. If residuals from the model are considered sufficiently skewed to violate the normality assumption, a Poisson regression with robust standard errors will be used. For these outcomes and for **time from randomisation to discharge from EPU care,** data will be summarized using means and standard deviations, as well as medians and inter-quartile ranges to aid the understanding of the data.

A template for reporting continuous outcomes is given in Appendix D7.2.

9.7. Analysis methods – exploratory outcomes and analyses

Any data that does not form a pre-specified outcome will be presented using simple summary statistics by treatment group (i.e. numbers and percentages for binary data and means (or medians) and standard deviations (or inter-quartile ranges) for continuous normal (or non-normal) data.

9.8. Safety data

Information for adverse events was captured in AE forms and categorised by CTCAE category[12] (v4.0). Only AEs graded 3, 4 or 5 were required to be reported for the MifeMiso trial.
Information for serious adverse events was captured in SAE forms and categorised by CTCAE category[12] (v4.0).

AEs (side effects) that occur with a frequency of >5% in at least one of the treatment groups will be summarised by treatment group using frequencies and percentages, and analysed as for all secondary binary outcomes, as detailed in section 9.6. All other AEs will be categorised as 'other' side effects and summarised only. See Appendix 9.1 for the template for reporting AEs.

The number and percentage of women experiencing any adverse event (AE, listed as side effects in secondary outcomes), any serious adverse event (SAE, listed as serious complications in secondary outcomes) and suspected unexpected serious adverse reaction (SUSAR) will be

presented by treatment group. The total number of AEs, SAEs and SUSARs in each treatment group will also be given, along with a descriptive table of the events including CTCAE category for reporting, date of onset, date resolved, severity, relatedness and the causality assessment by the site PI (or delegated clinician) and details of the event.

A template for reporting is given in Appendices D9.2, 9.3 and 9.4.

9.9. Planned subgroup analyses

Subgroup analyses will be limited to the same variables used as minimisation variables (please refer to Section 4.6; excluding centre). Tests for statistical heterogeneity (e.g. by including treatment group by subgroup interaction parameter in the final regression model) will be performed prior to any examination of effect estimate within subgroups. The subgroup defined by gestational age (<70, ≥70 days) is of special interest; the results of other subgroup analyses will be treated with caution, and used for the purposes of hypothesis generation only.[14] Analysis will be limited to the primary outcome measure only.

The effects of these subgroups will be examined by log-binomial regression model analysis, using independent variables as the interaction between treatment arm and each of the binary minimisation covariates (maternal age, BMI, previous parity, gestational age and amount of bleeding), separately for each subgroup analysis, together with their main effects. Where applicable, maternal age, body mass index and gestational age will be treated as continuous. The model will be adjusted for the clustering effect of randomising centres by using robust standard errors at centre level. The risk ratios and 95% confidence intervals and p-values for the interaction terms from the associated models will be presented. No adjustment for multiple testing will be made to the p-values for the interaction terms as we have pre-specified a subgroup of special interest and the results of all other subgroups analyses will be considered cautiously.

A template for reporting subgroup analyses is given in Appendix D8.

Sub-group related estimates and 95% confidence intervals may also be presented on a forest plot (see Figure 3).

9.10. Sensitivity analyses

Sensitivity analyses will be limited to the primary outcome and will consist of:

- a restricted analysis excluding women for whom the primary outcome was determined using information from the BERC review (i.e. women with available USS information only), to assess the robustness of the results that include clinical criteria for the primary outcome derivation.

- a multiple imputation approach[15] if the missing primary outcome data is >5% (i.e. after using BERC information to derive the primary outcome). Women in the MifeMiso

combination group and misoprostol alone group will be imputed separately, which would allow unbiased estimates for any interaction effects between the treatment and covariates in the analysis model. The imputation model will include all the minimisation variables: maternal age, body mass index, previous parity, gestational age, amount of bleeding and randomising centres where maternal age, body mass index and gestational age will be treated as continuous and be used to generate 20 simulated data-sets. Analyses will then be performed on each set with the results combined using Rubin's rules[16] to obtain a single set of results (treatment effect estimate and confidence intervals).

A template for reporting subgroup analyses is given in Appendix D6.

10. Analysis of sub-randomisations

Not applicable.

11. Health economic analysis

As indicated in the protocol there will also be a cost effectiveness analysis, based on the outcomes of cost per successfully managed miscarriage and cost per Quality-Adjusted Life Year (QUALY). The details of this analysis will be documented separately (see current version of the MifeMiso Protocol).

12. Statistical software

Stata version 12 (or higher) and/or SAS software, version 9.4 (or higher) will be used for all analyses.

13. References

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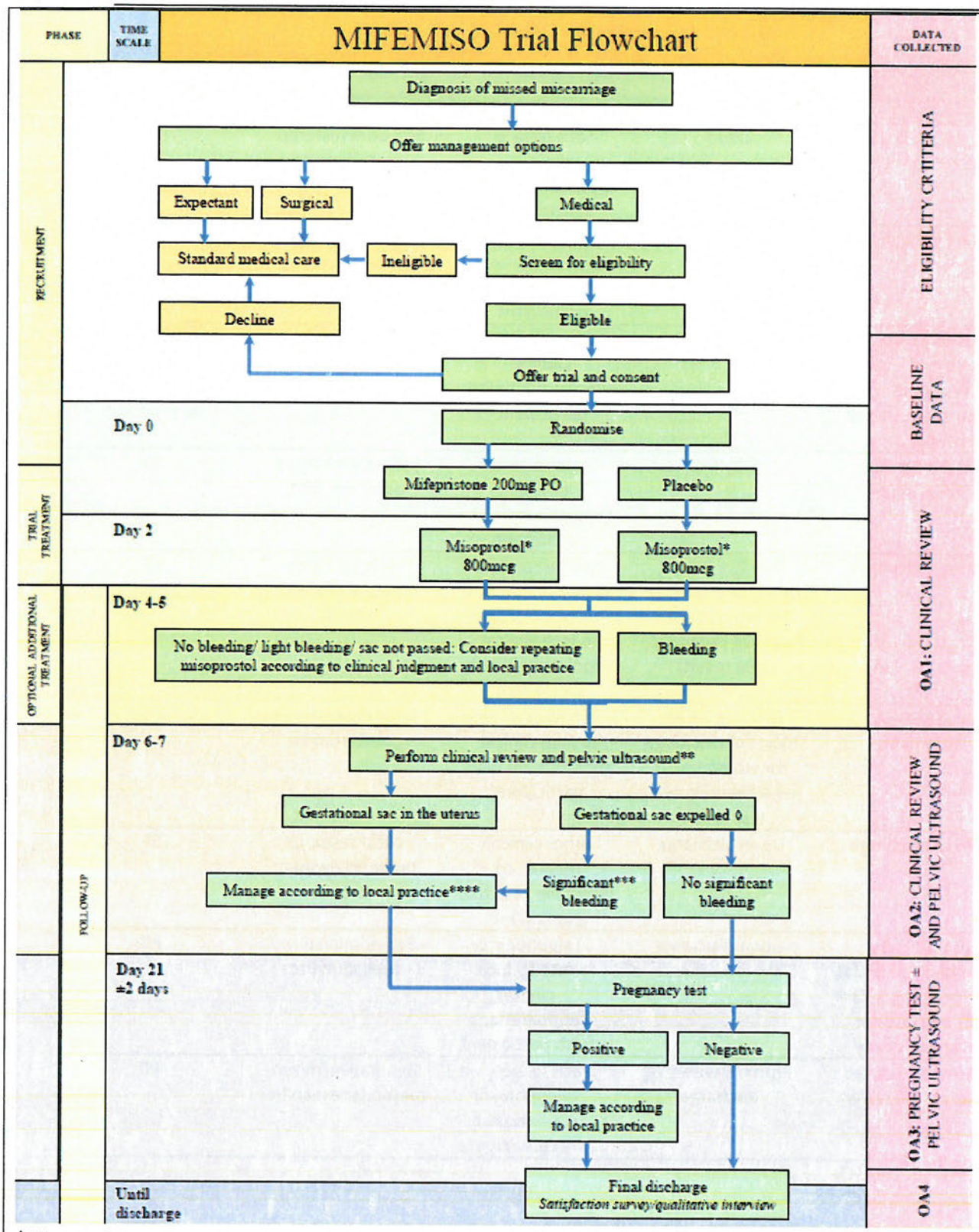
Appendix A – Deviations from SAP

This report below follows the statistical analysis plan dated <insert effective date of latest SAP> apart from the following:

Section of report not following SAP	Reason
<insert section >	<insert, e.g. exploratory analyses request by TMG>

Appendix B – Trial schema

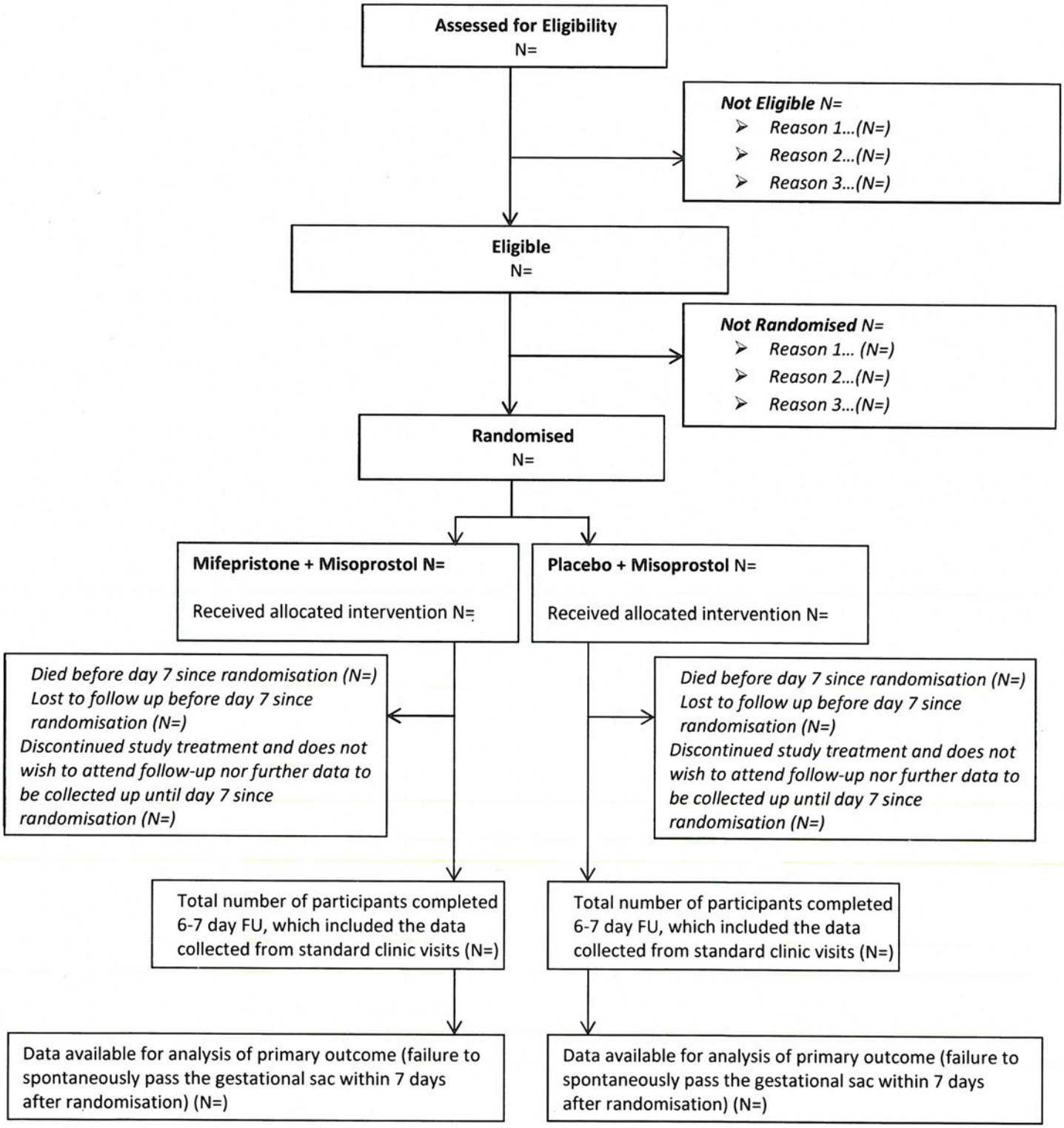


◊ Primary outcome.
* If gestational sac has been passed before the scheduled time for misoprostol, misoprostol can be omitted
** If scan performed earlier than day 6-7 and sac passed then repeat scan at day 6-7 not required
*** According to clinical judgment
**** Advice: Avoid surgical evacuation unless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

Appendix C – Schedule of assessments

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 participant	Self-administered questionnaire	PD
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

Appendix D1 – CONSORT flow diagram



Appendix D2 – Baseline characteristics

		Mifepristone + Misoprostol (N=)	Placebo + Misoprostol (N=)	Overall (N=)
Minimisation variables				
Maternal age (years)	< 30	N (%)	N (%)	N (%)
	≥ 30	N (%)	N (%)	N (%)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
	Median [IQR]	Median [IQR]	Median [IQR]	Median [IQR]
BMI (kg/m^2)	< 35	N (%)	N (%)	N (%)
	≥ 35	N (%)	N (%)	N (%)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
	Median [IQR]	Median [IQR]	Median [IQR]	Median [IQR]
Previous parity	Nulliparous	N (%)	N (%)	N (%)
	Parous women	N (%)	N (%)	N (%)
Gestational age (days)	< 70	N (%)	N (%)	N (%)
	≥ 70	N (%)	N (%)	N (%)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
	Median [IQR]	Median [IQR]	Median [IQR]	Median [IQR]
Amount of bleeding	PBAC score ≤2	N (%)	N (%)	N (%)
	PBAC score ≥3	N (%)	N (%)	N (%)
Other demographic and clinical characteristics				
Ethnicity	White	N (%)	N (%)	N (%)
	Black	N (%)	N (%)	N (%)
	Asian	N (%)	N (%)	N (%)
	Mixed	N (%)	N (%)	N (%)
	Other ethnic group	N (%)	N (%)	N (%)
	Missing	N (%)	N (%)	N (%)
Progesterone levels	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
	Median [IQR]	Median [IQR]	Median [IQR]	Median [IQR]
	Not measured	N (%)	N (%)	N (%)
	Missing	N (%)	N (%)	N (%)
Pregnancy-related pain score at randomisation[1]	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
	Median [IQR]	Median [IQR]	Median [IQR]	Median [IQR]
	Missing	N (%)	N (%)	N (%)
Number of gestational sacs	1	N (%)	N (%)	N (%)
	2	N (%)	N (%)	N (%)
	≥3	N (%)	N (%)	N (%)
	Missing	N (%)	N (%)	N (%)
Days from date of US diagnosing missed miscarriage to randomisation	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
	Median [IQR]	Median [IQR]	Median [IQR]	Median [IQR]
	Not measured	N (%)	N (%)	N (%)
	Missing	N (%)	N (%)	N (%)
Current concomitant medication	Yes	N (%)	N (%)	N (%)
	No	N (%)	N (%)	N (%)
	Missing	N (%)	N (%)	N (%)
If Yes, name of medication	<Name 1>	N (%)	N (%)	N (%)
	<Name 2>	N (%)	N (%)	N (%)
	<Name 3>	N (%)	N (%)	N (%)
	<Name 4>	N (%)	N (%)	N (%)

		Mifepristone + Misoprostol (N=)	Placebo + Misoprostol (N=)	Overall (N=)
Medical history				
Diabetes	Yes	N (%)	N (%)	N (%)
	No	N (%)	N (%)	N (%)
	Missing	N (%)	N (%)	N (%)
Renal disease	Yes	N (%)	N (%)	N (%)
	No	N (%)	N (%)	N (%)
	Missing	N (%)	N (%)	N (%)
Cardiac disease	Yes	N (%)	N (%)	N (%)
	No	N (%)	N (%)	N (%)
	Missing	N (%)	N (%)	N (%)
Chronic hypertension	Yes	N (%)	N (%)	N (%)
	No	N (%)	N (%)	N (%)
	Missing	N (%)	N (%)	N (%)
Thyroid disease	Yes	N (%)	N (%)	N (%)
	No	N (%)	N (%)	N (%)
	Missing	N (%)	N (%)	N (%)
Cancer	Yes	N (%)	N (%)	N (%)
	No	N (%)	N (%)	N (%)
	Missing	N (%)	N (%)	N (%)
Other	Yes	N (%)	N (%)	N (%)
	No	N (%)	N (%)	N (%)
	Missing	N (%)	N (%)	N (%)
Number of previous pregnancies				
Live birth	0	N (%)	N (%)	N (%)
	1	N (%)	N (%)	N (%)
	...	N (%)	N (%)	N (%)
	Missing	N (%)	N (%)	N (%)
Stillbirth	0	N (%)	N (%)	N (%)
	1	N (%)	N (%)	N (%)
	...	N (%)	N (%)	N (%)
	Missing	N (%)	N (%)	N (%)
Miscarriage	0	N (%)	N (%)	N (%)
	1	N (%)	N (%)	N (%)
	...	N (%)	N (%)	N (%)
	Missing	N (%)	N (%)	N (%)
Ectopic pregnancy	0	N (%)	N (%)	N (%)
	1	N (%)	N (%)	N (%)
	...	N (%)	N (%)	N (%)
	Missing	N (%)	N (%)	N (%)
Molar pregnancy	0	N (%)	N (%)	N (%)
	1	N (%)	N (%)	N (%)
	...	N (%)	N (%)	N (%)
	Missing	N (%)	N (%)	N (%)
Termination	0	N (%)	N (%)	N (%)
	1	N (%)	N (%)	N (%)
	...	N (%)	N (%)	N (%)
	Missing	N (%)	N (%)	N (%)
Pregnancy of unknown location	0	N (%)	N (%)	N (%)
	1	N (%)	N (%)	N (%)
	...	N (%)	N (%)	N (%)
	Missing	N (%)	N (%)	N (%)

[1] 0-10, 0 indicates no pain, 10 indicates worst possible pain.

Appendix D3 – Description of interventions

		Mifepristone + Misoprostol (N=)	Placebo + Misoprostol (N=)
Mifepristone or placebo taken	Yes	N (%)	N (%)
	No	N (%)	N (%)
	If no, reason:		
	Woman changed her mind	N (%)	N (%)
	Sac already passed	N (%)	N (%)
	Other	N (%)	N (%)
Misoprostol taken	Yes	N (%)	N (%)
	No	N (%)	N (%)
	If no, reason:		
	Woman changed her mind	N (%)	N (%)
	Woman did not attend hospital	N (%)	N (%)
	Sac already passed	N (%)	N (%)
	Other	N (%)	N (%)
If Yes, route of administration of first dose of misoprostol	PV	N (%)	N (%)
	PO	N (%)	N (%)
	Sublingual	N (%)	N (%)
	Missing	N (%)	N (%)
Additional doses of misoprostal taken	Yes	N (%)	N (%)
	1 additional dose	N (%)	N (%)
	2 additional doses	N (%)	N (%)
	≥ 3 additional doses	N (%)	N (%)
	Mean (SD)	Mean (SD)	Mean (SD)
	Median [IQR]	Median [IQR]	Median [IQR]
	No	N (%)	N (%)
	Missing	N (%)	N (%)
If Yes, route of administration of first additional dose	PV	N (%)	N (%)
	PO	N (%)	N (%)
	Sublingual	N (%)	N (%)
	Missing	N (%)	N (%)
If Yes, dose of first additional dose (mcg)	Mean (SD)	Mean (SD)	Mean (SD)
	Median [IQR]	Median [IQR]	Median [IQR]
	Missing	N (%)	N (%)
If Yes, days since mifepristone/placebo of first additional dose	Mean (SD)	Mean (SD)	Mean (SD)
	Median [IQR]	Median [IQR]	Median [IQR]
	Missing	N (%)	N (%)

Appendix D4 – Adherence to treatment allocation by group

	Mifepristone + Misoprostol (N=)	Placebo + Misoprostol (N=)
Number adherent with treatment regime[1]	N (%)	N (%)
Number non-adherent	N (%)	N (%)
Missing[2]	N (%)	N (%)

[1] 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 adherent to the trial medication as long as the allocated mifepristone/placebo is taken on day 0.

[2]Either the drug information was missing on day 0 or it was missing on day 2 if the allocated drug was taken on day 0. If the allocated drug was not taken on day 0 the woman will fall into the category of non-adherence.

Note: All figures presented are N (%) unless otherwise specified.

Appendix D5 – Protocol deviations by group

Protocol deviation	Mifepristone + Misoprostol (N=)	Placebo + Misoprostol (N=)
A		
B		
C		

Appendix D6 – Primary outcome results

	Mifepristone + Misoprostol (N=)	Placebo + Misoprostol (N=)	Adjusted risk ratio[1] (95% CI)	P-value
Failure to pass the gestational sac spontaneously within 7 days after randomisation				
Primary analysis				
Yes[2]	N (%)	N (%)		
No	N (%)	N (%)		
Missing	N	N		
Sensitivity analysis				
Excluding women requiring primary outcome information provided by Blinded Endpoint Review				
Yes[2]	N (%)	N (%)		
No	N (%)	N (%)		
Multiple imputation				
Yes[2]	N (%)	N (%)		
No	N (%)	N (%)		

[1]Value <1 favours MifeMiso combination group. The risk ratio was adjusted for minimisation variables: maternal age, body mass index, previous parity, gestational age and amount of bleeding. The clustering effect of randomising centres was accounted for by using robust standard errors at centre level.

[2]"Yes" means failed to pass the gestational sac spontaneously within 7 days after randomisation.

Note: All figures presented are N (%) unless otherwise specified.

Appendix D7.1 – Secondary outcome results (binary)

	Mifepristone + Misoprostol (N=)	**Placebo + Misoprostol** (N=)	Adjusted risk ratio[1] (95% CI)	P-value
Key secondary outcome:				
Surgical intervention to resolve the miscarriage up to discharge from EPU				
Yes[2]	N (%)	N (%)		
No	N (%)	N (%)		
Missing	N	N		
Reason for surgery				
Pregnancy tissue remaining	N (%)	N (%)		
Significant bleeding	N (%)	N (%)		
Other	N (%)	N (%)		
Missing	N (%)	N (%)		
Outcome of surgery				
Complicated	N (%)	N (%)		
Bleeding at surgery	N (%)	N (%)		
Uterine damage	N (%)	N (%)		
Need for extensive surgical intervention	N (%)	N (%)		
Other	N (%)	N (%)		
Missing	N (%)	N (%)		
Uncomplicated	N (%)	N (%)		
Missing	N (%)	N (%)		
Other secondary outcomes				
Surgical intervention to resolve the miscarriage up to and including day 7 post randomisation				
Yes[2]	N (%)	N (%)		
No	N (%)	N (%)		
Missing	N	N		
Surgical intervention to resolve the miscarriage after day 7 and up to discharge from EPU				
Yes[2]	N (%)	N (%)		
No	N (%)	N (%)		
Missing	N	N		
Need for further doses of misoprostol within 7 days after randomisation				
Yes[2]	N (%)	N (%)		
No	N (%)	N (%)		
Missing	N	N		
Need for further doses of misoprostol up to discharge from EPU care				
Yes[2]	N (%)	N (%)		
No	N (%)	N (%)		
Missing	N	N		
Infection requiring outpatient antibiotic treatment				
Yes[2]	N (%)	N (%)		
No	N (%)	N (%)		
	N	N		
Infection requiring inpatient antibiotic treatment				
Yes[2]	N (%)	N (%)		
No	N (%)	N (%)		
Missing	N	N		
Negative pregnancy test result 21 days (± 2 days) after randomisation				
Yes[2]	N (%)	N (%)		
No	N (%)	N (%)		

	Mifepristone + Misoprostol (N=)	**Placebo + Misoprostol** (N=)	Adjusted risk ratio[1] (95% CI)	P-value
Test not provided	N	N		
Missing	N	N		

[1]Value <1 favours MifeMiso combination group. The risk ratio was adjusted for minimisation variables: maternal age, body mass index, previous parity, gestational age and amount of bleeding. The clustering effect of randomising centres was accounted for by using robust standard errors at centre level.

[2]"Yes" means the corresponding outcome measure is true.

Note: All figures presented are N (%) unless otherwise specified.

Appendix D7.2 – Secondary outcomes (continuous)

	Mifepristone + Misoprostol (N=)	**Placebo + Misoprostol** (N=)	Adjusted Mean Difference[1] (95% CI)
Overall patient satisfaction score (CSQ-8)			
Mean (SD, N)			
Median [IQR]			
Duration of bleeding reported by woman (days)			
Mean (SD, N)			
Median [IQR]			
Time from randomisation to discharge from EPU care (days)			
Mean (SD, N)			
Median [IQR]			

[1]Value <0 favours MifeMiso combination treatment; adjusted for minimisation variables: maternal age, body mass index, previous parity, gestational age and amount of bleeding. The clustering effect of randomising centres was accounted for by using robust standard errors at centre level.

Appendix D7.3 – Concomitant medication post-randomisation

	Mifepristone + Misoprostol (N=)	**Placebo + Misoprostol** (N=)
Concomitant medication		
<Drug name 1>	N (%)	N (%)
<Drug name 2>	N (%)	N (%)
<Drug name 3>	N (%)	N (%)
<Drug name ....>	N (%)	N (%)

Appendix D8 – Subgroup analysis of the primary outcome

		Mifepristone + Misoprostol (N=)	Placebo + Misoprostol (N=)	Risk ratio (95% CI)[1]	P-value for interaction
Subgroups of special interest					
Gestational age (days)					
Gestational age <70	Yes[2]	N (%)	N (%)		
	No	N (%)	N (%)		
Gestational age ≥70	Yes[2]	N (%)	N (%)		
	No	N (%)	N (%)		
Exploratory subgroups					
Maternal age (years)					
Maternal age <30	Yes[2]	N (%)	N (%)		
	No	N (%)	N (%)		
Maternal age ≥ 30	Yes[2]	N (%)	N (%)		
	No	N (%)	N (%)		
Body mass index (BMI) (kg/m^2)					
BMI <35	Yes[2]	N (%)	N (%)		
	No	N (%)	N (%)		
BMI ≥35	Yes[2]	N (%)	N (%)		
	No	N (%)	N (%)		
Previous parity					
Nulliparous	Yes[2]	N (%)	N (%)		
	No	N (%)	N (%)		
Parous	Yes[2]	N (%)	N (%)		
	No	N (%)	N (%)		
Amount of bleeding					
PBAC score ≤2	Yes[2]	N (%)	N (%)		
	No	N (%)	N (%)		
PBAC score ≥3	Yes[2]	N (%)	N (%)		
	No	N (%)	N (%)		

[1]The risk ratios between MifeMiso combination group and Misoprostol alone group, 95% confidence intervals (CIs) and the corresponding p values were estimated from log-binomial regression models, after adjustment for the minimisation variables including maternal age, body mass index, previous parity, gestational age, amount of bleeding and the interaction effect between treatment and the corresponding subgroup covariate. The clustering effect of randomising centres was accounted for by using robust standard errors at centre level. Where appropriate, the main effects of minimisation variables including maternal age, body mass index and gestational age would be treated as continuous. Risk ratios <1 favors MifeMiso combination group.
[2]"Yes" means failed to pass the gestational sac spontaneously within 7 days after randomisation.

Figure 3: Forest plot for subgroup analyses

Appendix D9.1 – Safety outcomes

	Mifepristone + Misoprostol (N=)	Placebo + Misoprostol (N=)	Adjusted risk ratio[1] (95% CI)	P-value
Blood transfusion required[2]				
Yes	N (%)	N (%)		
No	N (%)	N (%)		
Any side effects (AEs)[2,3]				
Yes	N (%)	N (%)		
No	N (%)	N (%)		
Side effect 1[2]				
Yes	N (%)	N (%)		
No	N (%)	N (%)		
Side effect 2[2]				
Yes	N (%)	N (%)		
No	N (%)	N (%)		
Side effects 3[2]				
Yes	N (%)	N (%)		
No	N (%)	N (%)		
Side effects 4[2]				
Yes	N (%)	N (%)		
No	N (%)	N (%)		
Side effects 5[2]				
Yes	N (%)	N (%)		
No	N (%)	N (%)		
Side effects 6[2]				
Yes	N (%)	N (%)		
No	N (%)	N (%)		
Side effects 7[2]				
Yes	N (%)	N (%)		
No	N (%)	N (%)		
Side effects 8[2]				
Yes	N (%)	N (%)		
No	N (%)	N (%)		
Side effects 9[2]				
Yes	N (%)	N (%)		
No	N (%)	N (%)		
Side effects 10[2]				
Yes	N (%)	N (%)		
No	N (%)	N (%)		
Other side effects [2]				
Yes	N (%)	N (%)		
No	N (%)	N (%)		
Death[3]				
Yes	N (%)	N (%)		
No	N (%)	N (%)		
Any serious complications (SAEs)[2,3]				
Yes	N (%)	N (%)		
No	N (%)	N (%)		

[1]Value <1 favours MifeMiso combination group. The risk ratio was adjusted for minimisation variables: maternal age, body mass index, previous parity, gestational age and amount of bleeding. The clustering effect of randomising centres was accounted for by using robust standard errors at centre level.

[2]Collected up to discharge from EPU care

[3]Total number of women experiencing at least one AE/SAE

Appendix D9.2 – Adverse Events and Serious Adverse Events – total numbers

	Mifepristone + Misoprostol (N=)	**Placebo + Misoprostol** (N=)
Total number of women experiencing at least one AE –n (%)	n (%)	n (%)
Total number of AEs	n	n
Total number of women experiencing at least one SAE –n (%)	n (%)	n (%)
Total number of SAEs	n	n
Total number of women experiencing at least one SUSAR –n (%)	n (%)	n (%)
Total number of SUSARs	n	n

Appendix D9.3 – Adverse events – further details by group

	CTCAE category	Date of onset	Date resolved	Severity grade[1]	Causality	Details of event
Mifepristone + Misoprostol (N=)						
1						
2						
3						
4						
Placebo + Misoprostol (N=)						
1						
2						
3						
4						

[1] 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.

Appendix D9.4 – Serious Adverse Events – further details by group

	CTCAE category	Date of onset	Date resolved	Related to the intervention	Severity	Details of event
Mifepristone + Misoprostol (N=)						
1						
2						
3						
4						
Placebo + Misoprostol (N=)						
1						
2						
3						
4						