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

Summary

EudraCT number	2016-005097-35
Trial protocol	GB
Global end of trial date	13 January 2020

Results information

Result version number	v1 (current)
This version publication date	18 September 2020
First version publication date	18 September 2020

Trial information

Trial identification

Sponsor protocol code	RG_16-076

Additional study identifiers

ISRCTN number	ISRCTN17405024
ClinicalTrials.gov id (NCT number)	NCT03065660
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	Room 119, Aston Webb Building, Edgbaston, Birmingham, United Kingdom, B15 2TT
Public contact	Adam Devall, University of Birmingham, 44 07971823452, a.j.devall@bham.ac.uk
Scientific contact	Leanne Beeson, University of Birmingham, 44 01214149011, mifemiso@trials.bham.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 September 2019
Global end of trial reached?	Yes
Global end of trial date	13 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To test the hypothesis that in women diagnosed with missed miscarriage up to 13+6 weeks gestation, mifepristone (200mg orally) followed by misoprostol 800mcg taken vaginally, orally or sublingually two days later (MifeMiso) increases the passage of the gestational sac within seven days after randomisation, when compared to a placebo tablet with identical appearance to the mifepristone tablet followed by misoprostol 800mcg taken vaginally, orally or sublingually two days later.

Protection of trial subjects:

Patients undergoing medical management of miscarriage were already likely to be emotionally distressed
but were supported throughout their miscarriage management by their local early pregnancy units. This was the same for the trial participants. However, the subgroup of participants that agreed and consented to a semi-structured qualitative interview to discuss the treatment that they received could have experienced further emotional distress as a result of the interview. Participants who became more distressed during the interview were informed that they could stop the interview at any time and were signposted to their research nurse and/or regional and national miscarriage support resources. The discussion guide was also developed from the evidence base and was discussed in-depth with our PPI group to ensure that questions were appropriate phrased.

Background therapy:

In addition to the mifepristone (200mg orally) or matched placebo on day 0 and misoprostol (800mcg vaginally, orally or sublingually) on day 2 women may have received additional doses of misoprostol (as appropriate and according to local practice) if the gestational sac did not pass by day seven. Women may also have received surgical management if they opted for this. Women may have also been given an anti-emetic when taking the trial medication in order to prevent vomiting and pain relieving drugs (according to local practice).

Evidence for comparator:

Before the NICE guideline CG154 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. This recommendation was based on very limited evidence from one study of 115 women, which found no difference between MifeMiso combination and misoprostol alone. Recognising the limited available evidence, the NICE guideline and HTA called for a trial to compare the clinical and cost effectiveness of mifepristone plus misoprostol versus misoprostol alone for the medical management of missed miscarriage.

A dose of 200mg was used for mifepristone 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. Misoprostol 800mcg was administered according to local practice (orally, vaginally or sublingually).

Actual start date of recruitment	20 September 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 711
Worldwide total number of subjects	711
EEA total number of subjects	711

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	2
Adults (18-64 years)	709
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The participants in the MifeMiso trial were recruited from 28 hospitals located across the United Kingdom between October 2017 and July 2019.

Pre-assignment

Screening details:

Women were eligible if they were aged 16 years and over, diagnosed with a missed miscarriage by pelvic ultrasound scan in the first 13+6 weeks of pregnancy, chose to have medical management of miscarriage and were willing and able to give informed consent. 2746 women were assessed for eligibility, 2595 were eligible and 711 were randomised.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

Participants were randomly assigned in a 1:1 ratio to a single dose of oral mifepristone 200mg, followed by a single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later, or an oral placebo tablet followed by a single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later. The placebo was manufactured by ModePharma Ltd. to be identical to the mifepristone tablet.

Arms

Are arms mutually exclusive?	Yes
Arm title	Mifepristone plus misoprostol

Arm description:

A single dose of oral mifepristone 200mg, followed by a single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later.

Arm type	Experimental
Investigational medicinal product name	Mifepristone
Investigational medicinal product code	SUB08956MIG
Other name	Mifegyne
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Single dose of oral mifepristone 200mg

Investigational medicinal product name	Misoprostol
Investigational medicinal product code	PL 00057/0956
Other name	
Pharmaceutical forms	Tablet + vaginal tablet
Routes of administration	Oral use, Sublingual use, Vaginal use

Dosage and administration details:

Single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later

Arm title	Placebo plus misoprostol

Arm description:

An oral placebo tablet followed by a single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Single placebo tablet

Investigational medicinal product name	Misoprostol
Investigational medicinal product code	PL 00057/0956
Other name	
Pharmaceutical forms	Tablet + vaginal tablet
Routes of administration	Oral use, Sublingual use, Vaginal use

Dosage and administration details:

Single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later

Number of subjects in period 1	Mifepristone plus misoprostol	Placebo plus misoprostol
Started	357	354
Completed	348	348
Not completed	9	6
Lost to follow-up	6	3
Discontinued study treatment & not want follow up	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Mifepristone plus misoprostol
Reporting group description:	
A single dose of oral mifepristone 200mg, followed by a single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later.	
Reporting group title	Placebo plus misoprostol
Reporting group description:	
An oral placebo tablet followed by a single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later	

Reporting group values	Mifepristone plus misoprostol	Placebo plus misoprostol	Total
Number of subjects	357	354	711
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	1	1	2
Adults (18-64 years)	356	353	709
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	32.8	32.7	
standard deviation	± 5.6	± 5.7	-
Gender categorical Units: Subjects			
Female	357	354	711
Male	0	0	0
Body Mass Index Units: Subjects			
<35	332	328	660
≥35	25	26	51
Previous parity Units: Subjects			
Nulliparous	167	168	335
Parous	190	186	376
Gestational age in days Units: Subjects			
<70	176	175	351
≥70	181	179	360
Amount of bleeding (Pictorial Blood Assessment Chart score) Units: Subjects			

≤2	351	348	699
≥3	6	6	12
Ethnic group Units: Subjects			
White	296	280	576
Black	10	17	27
South Asian	38	42	80
Other	13	15	28
Number of gestational sacs Units: Subjects			
One	351	348	699
Two	6	6	12
Previous live birth Units: Subjects			
Zero	176	174	350
One	111	118	229
Two	45	39	84
≥ Three	25	23	48
Previous stillbirth Units: Subjects			
Zero	351	350	701
One	6	3	9
Two	0	1	1
Previous miscarriage Units: Subjects			
Zero	233	225	458
One	62	77	139
Two	29	24	53
≥ Three	33	28	61
Previous ectopic pregnancy Units: Subjects			
Zero	344	345	689
One	13	9	22
Previous molar pregnancy Units: Subjects			
Zero	357	353	710
One	0	1	1
Previous termination Units: Subjects			
Zero	304	296	600
One	44	45	89
Two	7	10	17
≥ Three	2	3	5
Previous pregnancy of unknown location Units: Subjects			
Zero	354	354	708
One	3	0	3
Pregnancy-related pain score at randomization Units: Pain score			
arithmetic mean	1.0	1.2	

standard deviation	± 1.8	± 2.0	-
Progesterone levels			
Units: nmol/L			
arithmetic mean	17.0	22.8	
standard deviation	± 4.2	± 12.8	-
Days from date of ultrasound scan diagnosing missed miscarriage to randomisation			
Units: days			
arithmetic mean	1.5	1.9	
standard deviation	± 3.3	± 4.6	-

End points

End points reporting groups

Reporting group title	Mifepristone plus misoprostol
Reporting group description:	
A single dose of oral mifepristone 200mg, followed by a single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later.	
Reporting group title	Placebo plus misoprostol
Reporting group description:	
An oral placebo tablet followed by a single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later	

Primary: Failure to pass the gestational sac spontaneously within 7 days after randomisation

End point title	Failure to pass the gestational sac spontaneously within 7 days after randomisation
End point description:	
End point type	Primary
End point timeframe:	
Within 7 days after randomisation	

End point values	Mifepristone plus misoprostol	Placebo plus misoprostol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	348	348		
Units: Subjects	59	82		

Statistical analyses

Statistical analysis title	Primary outcome analysis
Comparison groups	Mifepristone plus misoprostol v Placebo plus misoprostol
Number of subjects included in analysis	696
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.99

Secondary: Surgical intervention to resolve the miscarriage up to discharge

End point title	Surgical intervention to resolve the miscarriage up to discharge

End point description:

End point type	Secondary

End point timeframe:

From time of randomisation up to discharge

End point values	Mifepristone plus misoprostol	Placebo plus misoprostol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	355	353		
Units: Subjects	62	87		

Statistical analyses

Statistical analysis title	Key secondary outcome analysis
Comparison groups	Mifepristone plus misoprostol v Placebo plus misoprostol
Number of subjects included in analysis	708
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	0.95

Secondary: Surgical intervention to resolve the miscarriage up to and including day 7 post randomisation

End point title	Surgical intervention to resolve the miscarriage up to and including day 7 post randomisation

End point description:

End point type	Secondary

End point timeframe:

Up to and including day 7 post randomization

End point values	Mifepristone plus misoprostol	Placebo plus misoprostol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	355	353		
Units: Subjects	23	19		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Comparison groups	Placebo plus misoprostol v Mifepristone plus misoprostol
Number of subjects included in analysis	708
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	2.21

Secondary: Surgical intervention to resolve the miscarriage from after day 7 and up to discharge

End point title	Surgical intervention to resolve the miscarriage from after day 7 and up to discharge

End point description:

End point type	Secondary

End point timeframe:

After day 7 from randomisation and up to discharge

End point values	Mifepristone plus misoprostol	Placebo plus misoprostol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	355	353		
Units: Subjects	39	68		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Comparison groups	Mifepristone plus misoprostol v Placebo plus misoprostol
Number of subjects included in analysis	708
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	0.81

Secondary: Need for further doses of misoprostol within 7 days after randomisation

End point title	Need for further doses of misoprostol within 7 days after randomisation
End point description:	
End point type	Secondary
End point timeframe:	
Within 7 days after randomization	

End point values	Mifepristone plus misoprostol	Placebo plus misoprostol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	356	354		
Units: Subjects	34	48		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Comparison groups	Mifepristone plus misoprostol v Placebo plus misoprostol
Number of subjects included in analysis	710
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.08

Secondary: Need for further doses of misoprostol up to discharge

End point title	Need for further doses of misoprostol up to discharge

End point description:

End point type	Secondary

End point timeframe:

From randomisation up to discharge

End point values	Mifepristone plus misoprostol	Placebo plus misoprostol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	357	354		
Units: Subjects	50	65		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Comparison groups	Mifepristone plus misoprostol v Placebo plus misoprostol
Number of subjects included in analysis	711
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.09

Secondary: Infection requiring outpatient antibiotic treatment

End point title	Infection requiring outpatient antibiotic treatment

End point description:

End point type	Secondary

End point timeframe:

From randomisation up to discharge

End point values	Mifepristone plus misoprostol	Placebo plus misoprostol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	351	351		
Units: Subjects	8	11		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Comparison groups	Mifepristone plus misoprostol v Placebo plus misoprostol
Number of subjects included in analysis	702
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	1.82

Secondary: Infection requiring inpatient antibiotic treatment

End point title	Infection requiring inpatient antibiotic treatment
End point description:	
End point type	Secondary
End point timeframe:	
From randomisation up to discharge	

End point values	Mifepristone plus misoprostol	Placebo plus misoprostol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	351	351		
Units: Subjects	5	4		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Comparison groups	Mifepristone plus misoprostol v Placebo plus misoprostol

Number of subjects included in analysis	702
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	4.74

Secondary: Negative pregnancy test result 21 days (± 2 days) after randomisation

End point title	Negative pregnancy test result 21 days (± 2 days) after randomisation
End point description:	

End point type	Secondary
End point timeframe:	
21 days (± 2 days) after randomisation	

End point values	Mifepristone plus misoprostol	Placebo plus misoprostol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	308	302		
Units: Subjects	237	230		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Comparison groups	Mifepristone plus misoprostol v Placebo plus misoprostol
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.14

Secondary: Duration of bleeding reported by woman

End point title	Duration of bleeding reported by woman

End point description:

End point type	Secondary

End point timeframe:

From randomisation up until discharge

End point values	Mifepristone plus misoprostol	Placebo plus misoprostol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	326	330		
Units: Days				
arithmetic mean (standard deviation)	16 (± 12.6)	16.3 (± 15.2)		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Comparison groups	Mifepristone plus misoprostol v Placebo plus misoprostol
Number of subjects included in analysis	656
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	1.8

Secondary: Time from randomisation to discharge

End point title	Time from randomisation to discharge

End point description:

End point type	Secondary

End point timeframe:

From randomisation up until discharge

End point values	Mifepristone plus misoprostol	Placebo plus misoprostol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	340	337		
Units: Days				
arithmetic mean (standard deviation)	27 (± 14.2)	27.3 (± 14.4)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From randomisation up until discharge

Adverse event reporting additional description:

Specific adverse events 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, were collected and recorded.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.2

Reporting groups

Reporting group title	Mifepristone plus misoprostol

Reporting group description:

A single dose of oral mifepristone 200mg, followed by a single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later.

Reporting group title	Placebo plus misoprostol

Reporting group description:

An oral placebo tablet followed by a single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: There were no non-serious adverse events that occurred at a frequency of >5%, therefore there are no events to be reported.

Serious adverse events	Mifepristone plus misoprostol	Placebo plus misoprostol	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 357 (1.40%)	2 / 354 (0.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Surgical and medical procedures			
Haemorrhage in pregnancy	Additional description: Significant haemorrhage of 2400mls, required surgical intervention. Participant received blood transfusion of 2 units		
subjects affected / exposed	1 / 357 (0.28%)	0 / 354 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Haemorrhage in pregnancy	Additional description: 1 x participant received 2 units of blood after large blood loss. Discharged home with Hb of 100, ERPC, bleeding settled. 1 x participant had emergency surgery and required 5 units of blood. Heavy vaginal bleeding leading to hypovolaemic shock		
subjects affected / exposed	0 / 357 (0.00%)	2 / 354 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ruptured ectopic pregnancy	Additional description: Participant underwent laparoscopic salpingectomy. Undiagnosed ectopic pregnancy at initial USS		
subjects affected / exposed	1 / 357 (0.28%)	0 / 354 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia of pregnancy	Additional description: Participant experienced fainting episodes and dizziness. Clinical appearance of anaemia following bleeding from miscarriage. Received 2 units of blood and prescribed ferrous sulphate		
subjects affected / exposed	1 / 357 (0.28%)	0 / 354 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Embolism arterial	Additional description: Embolism of uterine artery due to complications from fibroid uterus and surgical management of miscarriage. Arteriovenous malformation of fibroid. Uterine artery embolisation and hysterectomy performed.		
subjects affected / exposed	1 / 357 (0.28%)	0 / 354 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Chronic renal disease	Additional description: Participant had 2 units of blood transfused due to pre-existing chronic renal disease causing anaemia complicated by 250mls blood loss. Participant had a surgical management of miscarriage due to poor renal function and risk of further bleeding.		
subjects affected / exposed	1 / 357 (0.28%)	0 / 354 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Mifepristone plus misoprostol	Placebo plus misoprostol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 357 (0.00%)	0 / 354 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2017	The following changes were made to the protocol: 1. Addition of 'amount of bleeding (PBAC score; ≤2, ≥3)' as a stratification variable 2. Addition of a statement confirming women that have already participated in MifeMiso once cannot participate a second time
01 March 2017	The following changes were made to the protocol: 1. Addition of ISRCTN and Clinical Trials.gov number 2. Clarification regarding emergency unblinding 3. Addition of rationale for using stated doses of mifepristone and misoprostol 4. Amendment to statements regarding assessment of severity and causality of SAEs 5. Clarification regarding vaginal bleeding as an event not reportable as an SAE 6. 'Resolution of miscarriage' amended to 'discharge' in table 5 7. Clarification that day 21 ± 2 is the point of discharge for women with a negative pregnancy test result 8. Clarification regarding additional EQ-5D-5L questionnaire to be completed by women with an initial positive pregnancy test result 9. Clarification regarding compliance monitoring 10. Clarification regarding primary and secondary endpoint analyses
09 February 2018	The following changes were made to the protocol: 1. Change of contact details for trial personnel 2. Clarification of primary and secondary outcomes 3. Addition of sublingual route for misoprostol administration 4. 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 5. Clarification that the screening log is accessible through the online randomisation system 6. Clarification of storage temperature for IMP 7. Clarification of ways in which CSQ-8 questionnaire (satisfaction survey) is administered i.e paper and electronic 8. 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 9. Clarification of the end of trial definition 10. Clarification that qualitative interviews may be conducted via video call software e.g. Skype
27 June 2019	The following changes were made to the protocol: 1. Update to trial team contact details 2. Update to secondary outcomes and objectives 3. Reclassification of some secondary outcomes as safety outcomes 4. Clarification regarding unblinding 5. Update to health economic evaluation section 6. Addition of section regarding Blinded Endpoint Review Committee 7. Update to statistical analysis section

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

We studied the effect in missed miscarriage; therefore, these results are not generalisable to patients diagnosed with incomplete miscarriage. The rationale for this is the anti-progestogenic effect of mifepristone is less likely to have an effect.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32853559