National Institute for Health and Care Excellence

Final

Ectopic pregnancy and miscarriage

[D] Medical management of miscarriage

NICE guideline number NG126 (update)

Evidence review underpinning recommendations 1.5.11 to 1.5.19 in the NICE guideline

August 2023

Final

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Review question

Is the combination of mifepristone and misoprostol more effective than misoprostol alone in the medical management of missed miscarriage?

Introduction

During the development of the NICE guideline on ectopic pregnancy and miscarriage in 2019 the committee considered evidence on medication for the effective management of missed miscarriage, defined as a non-viable pregnancy identified on ultrasound scan during the first 14 weeks of gestation but all pregnancy tissue is retained in the uterus. While there was evidence for the effectiveness of misoprostol there was only very limited evidence for the combination of mifepristone and misoprostol from a pilot study. The committee therefore agreed not to recommend the combination but instead made a research recommendation. In 2020 a UK multi-centre randomised controlled trial addressed this research question. Called MifeMiso (Chu 2020) this study compared the effectiveness of mifepristone and misoprostol with misoprostol alone for the management of missed miscarriage.

The aim of this review is to examine the evidence from the MifeMiso study and identify the effectiveness of the combination of mifepristone and misoprostol for the management of missed miscarriage.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	• Women diagnosed with a missed miscarriage by pelvic ultrasound scan in the first 14 weeks of pregnancy Population excludes: • Women with a diagnosis of incomplete miscarriage • Women opting for alternative methods of miscarriage management (expectant or surgical) • Life threatening bleeding
Intervention	• Mifepristone and misoprostol in combination
Comparison	• Misoprostol and placebo
Outcome	**Critical** • Failure to spontaneously pass the gestational sac within 7 days after random assignment. • Surgical intervention to complete the miscarriage up to discharge from hospital care. **Important** • Surgical intervention to complete the miscarriage up to and including 7 days after random assignment. • Surgical intervention to complete the miscarriage from after day 7 • and up to discharge • Need for further doses of misoprostol within 7 days after random assignment. • Need for further doses of misoprostol up to discharge. • Infection requiring outpatient antibiotic treatment. • Infection requiring inpatient antibiotic treatment. • Negative pregnancy test result 21 days (±2 days) after random assignment. • Duration of bleeding as reported by the participant (days). • Requirement for blood transfusion. • Side-effects. • Any serious complications. • Maternal death
Study design	• RCT

RCT: Randomised control trial

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. The decision making process for a targeted review is described in appendix N of the NICE manual. Methods specific to this review question are described below.

Minimally important differences (MID) were used to assess clinically important differences. Cut-offs of confidence intervals of 0.8 and 1.25 were used for dichotomous outcomes and for continuous outcomes 0.5x the SD of the control group was used. Outcomes were considered to have an important benefit or harm, no evidence of an important difference, or no important difference using the following approach:

- Point estimate (PE) > +MID, 95% CI do not cross line of no effect = important benefit
- Point estimate (PE) > +MID, 95% CI cross the line of no effect = no evidence of an important difference.

- Point estimate (PE) between two MIDs = no important difference.
- Point estimate (PE) < -MID, 95% CI cross the line of no effect = no evidence of an important. Difference
- Point estimate (PE) < -MID, 95% CI do not cross line of no effect = important harm

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

This review is a targeted review. No literature search was conducted for this review and a study identified by the surveillance report has been included. One randomised control trial (Chu 2020) was included in this review. This study compared 200 mg oral mifepristone plus 800 micrograms vaginal, oral, or sublingual misoprostol to oral placebo plus 800 micrograms vaginal, oral, or sublingual misoprostol in women diagnosed with a missed miscarriage by pelvic ultrasound scan in the first 14 weeks of pregnancy (by last menstrual period) and who chose to have medical management of miscarriage.

The included study is summarised in Table 2.

Excluded studies

There are no excluded studies for this review as no literature search was conducted.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies.

Study	Population	Intervention	Comparison	Outcomes	Comment
Chu 2020 Randomised Control Trial UK (Multi-Centre- 28 UK hospitals)	N=711 Mifepristone plus misoprostol group: n= 357 Placebo plus misoprostol group: n= 354 **Maternal age (years):** Mifepristone plus misoprostol group: 32.8 ± 5.6 Placebo plus misoprostol group: 32.7 ± 5.5 **BMI (kg/m^2):** Mifepristone plus misoprostol group: 25.8 ± 5.6 Placebo plus misoprostol group: 26.5 ± 5.5	200mg oral Mifepristone plus 800 micrograms vaginal, oral, or sublingual misoprostol	Oral placebo plus 800 micrograms vaginal, oral, or sublingual misoprostol	• Failure to spontaneously pass the gestational sac within 7 days after random assignment. • Surgical intervention to complete the miscarriage up to discharge from hospital care. • Surgical intervention to complete the miscarriage up to and including 7 days after random assignment. • Surgical intervention to complete the miscarriage from after day 7 and up to discharge. • Need for further doses of misoprostol within 7 days after random assignment. • Need for further doses of misoprostol up to discharge. • Infection requiring outpatient antibiotic treatment. • Infection requiring inpatient antibiotic treatment. • Negative pregnancy test result 21 days (±2 days) after random assignment. • Duration of bleeding as reported by the participant. • Requirement for blood transfusion. • Side-effects. • Any serious complications. • Maternal death.	• Follow up time was unclear for some outcomes • Details of adverse and serious adverse events were not reported

BMI: Body Mass Index

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Summary of the evidence

Evidence from one RCT comparing mifepristone plus misoprostol versus placebo plus misoprostol suggested that there was important benefit for the combination therapy for the following outcomes: failure to spontaneously pass the gestational sac within 7 days after random assignment; surgical intervention to complete the miscarriage up to discharge from hospital care and surgical intervention to complete the miscarriage from after day 7 and up to discharge from hospital care. For all other outcomes (surgical intervention to complete the miscarriage up to and including 7 days after random assignment; need for further doses of misoprostol within 7 days after random assignment and; up to discharge; infection requiring outpatient antibiotic treatment; infection requiring inpatient antibiotic treatment; negative pregnancy test result 21 days (±2 days) after random assignment; duration of bleeding reported by the woman; requirement for blood transfusion; side-effects; any

serious complications; maternal death) there was either no evidence of an important difference or no important difference.

The quality of the evidence across all outcomes ranged from low to high with the critical outcomes being rated as moderate quality and most concerns were around imprecision.

See appendix F for full GRADE tables.

Economic evidence

Included studies

This review is a targeted review. No literature search was conducted for this review, with only papers identified by the surveillance report included. One economic study (Devall 2021) was included in this review.

Excluded studies

There are no excluded studies for this review as no literature search was conducted.

Summary of included economic evidence

See Table 3 for the economic evidence profile of the included study.

Table 3: Economic evidence profile of a targeted review of economic evaluations of mifepristone and misoprostol compared to misoprostol alone in the medical management of missed miscarriage

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effectiveness	
Devall 2021 Mifepristone and misoprostol versus placebo and misoprostol for resolution of miscarriage in women diagnosed with missed miscarriage: the MifeMiso RCT	Minor limitations	Directly applicable	Economic evaluation alongside RCT	Mifepristone and misoprostol -£182	0.0004 QALYs	Mifepristone and misoprostol dominate	Monte Carlo simulation using non-parametric bootstrapping of mean QALYs, and costs suggested there was a greater than 50% probability that Mifepristone and misoprostol was cost-effective

[1] Modelling was undertaken over a short time horizon and no probabilistic sensitivity analysis was conducted.
[2] Specific costs and disutilities of drug-related adverse events could not be explicitly modelled. Adverse events were captured by modelling treatment-specific withdrawal rates. This may have overestimated the cost effectiveness of maintenance treatment.
[3] The cost-effectiveness model was designed to reflect the management of Crohn's disease in the Swedish healthcare setting. Although a cost per QALY estimate was reported, it was not based on health-related quality of life values elicited from patients.

Economic model

No economic modelling was undertaken for this review because surveillance had identified a recent and applicable UK economic evaluation which could be used to assess cost-effectiveness.

Unit costs

Resource	Unit costs	Source
Mifepristone 200 mg tablet	£17.55	BNF https://bnf.nice.org.uk/drugs/mifepristone/medicinal-forms/ (accessed May 2023)
Misoprostol 800 microgram (2 x 400 microgram)	£16.00	BNF https://bnf.nice.org.uk/drugs/misoprostol/medicinal-forms/ (accessed May 2023)
Mifepristone 200 mg oral tablet and 4 x misoprostol 200 micrograms vaginal tablets (Medabon combipack)	£17	BNF https://bnf.nice.org.uk/drugs/mifepristone-and-misoprostol/medicinal-forms/ (accessed May 2023)

The committee's discussion and interpretation of the evidence

The outcomes that matter most

The aim of this review was to determine the effectiveness of the administration of mifepristone and misoprostol compared to misoprostol and placebo for the medical management of missed miscarriage.

As this is a targeted review that includes only one study identified by surveillance, the outcomes that matter the most have been taken from this study. These outcomes have been categorised as critical if they were specified as primary outcomes or as important if they were key secondary outcomes and these critical and important outcomes provide the most direct information about the effectiveness of the treatment to complete the miscarriage process.

The critical outcomes for this review are failure to spontaneously pass the gestational sac within 7 days after random assignment and surgical intervention to complete the miscarriage up to discharge from hospital care.

The important outcomes for this review are those that were categorised as secondary outcomes by the study and these provide additional detail about the benefits and possible harms of the treatments being investigated. The important outcomes for this review are; surgical intervention to complete the miscarriage up to and including 7 days after random assignment and from after day 7 up to discharge; need for further doses of misoprostol within 7 days after random assignment and up to discharge; infection requiring outpatient antibiotic treatment; infection requiring inpatient antibiotic treatment; negative pregnancy test result 21 days (±2 days) after random assignment; duration of bleeding as reported by the participant and requirement for blood transfusion. The additional outcomes of side-effects, any serious complications and maternal death have also been included. Evidence was available for all the above critical and important outcomes.

The quality of the evidence

The overall rating of the included RCT was high quality. This was a large double-blind trial so the risk of bias due to deviations from the intended intervention was low. The quality of the evidence ranged from low to high. The evidence from the critical outcomes was of moderate quality and the evidence from the important outcomes ranged from low to high. Outcomes were only downgraded for imprecision. The committee took into account the quality of the evidence, including the uncertainty in their interpretation of the evidence.

Benefits and harms

The committee's discussion focused on the evidence for the use of mifepristone in combination with misoprostol for the treatment of missed miscarriage as the included trial did not provide evidence for use in incomplete miscarriage. A missed miscarriage is diagnosed when a non-viable pregnancy is identified on ultrasound scan during the first 14 weeks of gestation but all pregnancy tissue is retained in the uterus.

The committee discussed that the evidence clearly supports the use of the combination of mifepristone with misoprostol for the management of missed miscarriage, as a more clinically and cost effective treatment than misoprostol alone and that the combination should be offered to women at the doses stated in the evidence. They acknowledged that there was some uncertainty around the point estimates. They based their decision on the moderate quality evidence for the critical outcomes and one important outcome, suggesting an important benefit for the outcomes failure to pass the gestational sac after 7 days and need for surgical intervention to complete the miscarriage up to discharge, or from 7 days to discharge. The committee agreed that there was no evidence of difference for any other outcomes, and no evidence of negative effects from low to high quality evidence for mifepristone in combination with misoprostol compared to misoprostol and placebo for all the outcomes relating to possible harms (for example infection, bleeding, side-effects of the medication, or maternal death). This allowed them to make a strong recommendation.

The committee also noted that both mifepristone and misoprostol were not approved for use in the treatment of missed miscarriage, but were approved for termination of pregnancy. However, the mode of action would be the same in both conditions and so the committee agreed to recommend the combination for missed miscarriage

The committee had some concerns about the lack of a lower limit for the timing of the pelvic ultrasound scan that was used to diagnose missed miscarriage because there is the potential for error in pregnancies that are under 8 weeks' gestation as it is more difficult to diagnose miscarriage at that timepoint due to the crown to rump length potentially being less than 7mm. The committee emphasised the importance of having two ultrasonographers to reduce the chance of an incorrect diagnosis. The committee then discussed that it was reassuring that the included trial had conducted a subgroup analysis for pregnancies greater than or less than 70 days' gestation and found no evidence of a subgroup effect.

The evidence had not included women diagnosed with incomplete miscarriage. The committee discussed that evidence for missed miscarriage cannot be extrapolated to women diagnosed with incomplete miscarriage. However, the committee agreed that a research recommendation was not needed for incomplete miscarriage as mifepristone primes the uterus to the action of misoprostol, which causes uterine contractions and expulsion of the products of conception. In an incomplete miscarriage, the expulsion of the products of conception has already begun, so the use of mifepristone is not required, and the use of misoprostol alone is sufficient.

The committee discussed the importance of advising women and people experiencing miscarriage about the process which would occur after taking the medication and what to expect. The committee emphasised the need to have an open and clear discussion as it is important that women and people experiencing miscarriage are supported throughout the process and not left to cope alone after medical management. Based on the timings used in the evidence and their knowledge and experience the committee recommended that women and people experiencing miscarriage should contact their healthcare professional if bleeding had not started 48 hours after taking misoprostol. The committee also discussed the need for units to be able make alternative follow up arrangements for women and people experiencing miscarriage who would not or could not contact the unit. Based on their knowledge and experience, the committee also agreed that women and people who are experiencing

miscarriage should be given advice on when and how to seek help during the miscarriage process.

The committee acknowledged the importance of follow-up for women and people experiencing miscarriage with a positive pregnancy test at 3 weeks as this would indicate the treatment had not been successful. They also discussed the importance of follow up for women and people with worsening symptoms such as bleeding, in order to be able to assess their need for further investigations or treatment. These people should be reviewed by a health care professional to rule out retained pregnancy tissue and to assess the need for any further investigations or management strategies.

The committee agreed, based on their knowledge and experience, that although a complete molar or ectopic pregnancy (including a heterotopic pregnancy) should have been ruled out before the medical management of miscarriage began this may need to be considered as a potential diagnosis if the pregnancy test was still positive after 3 weeks. Based on stakeholder feedback, the committee also added an additional recommendation to state that even if the pregnancy test was negative, if the woman or person still had heavy bleeding or other symptoms they would require further investigation.

The committee considered whether units should provide pregnancy tests for women and people experiencing miscarriage to use after 3 weeks or if they should advise people to buy their own urine pregnancy test to use at home. They noted that the current recommendations on expectant management of miscarriage required women and people experiencing miscarriage to obtain their own pregnancy test, whereas the guidance following medical management advised that women and people having a miscarriage should be supplied with a pregnancy test. To ensure parity of treatment between all groups experiencing miscarriage, the committee recommended that units treating women with miscarriage should provide a urine pregnancy test to use after 3 weeks for both expectant and medical management.

Cost effectiveness and resource use

The committee were aware of one study (Devall 2021) that found that mifepristone plus misoprostol led to significantly reduced costs of £182 per woman (95% confidence interval £26 to £338) when compared to placebo plus misoprostol for the medical management of missed miscarriage. This was because reduced surgery and hospital visits more than offset the higher intervention costs of mifepristone plus misoprostol. The analysis also reported that mifepristone plus misoprostol also resulted in a statistically significant increase in successfully managed miscarriages and therefore it was concluded that mifepristone plus misoprostol dominated placebo plus misoprostol.

Therefore, the committee concluded that there was strong cost effectiveness evidence to support their recommendation to offer 200 mg oral mifepristone, and 48 hours later, 800 micrograms misoprostol (vaginal, oral or sublingual), unless the gestational sac has already been passed, for the medical management of missed miscarriage.

As missed miscarriage affects approximately 1-5% of pregnancies (Levono 2013) this would be approximately 6,000 to 30,000 pregnancies in the NHS. The committee did not think that their recommendation would have a significant resource impact to the NHS (>£1 million) even when only the intervention cost is taken into account. Overall, the committee considered that their recommendation would be cost saving to the NHS as a result of reduced surgery and hospital visits.

The committee noted that the recommendations now advised people to contact their healthcare professional if bleeding had not started 48 hours after the misoprostol (previously this recommendation had advised after 24 hours) so this may reduce resource use, but that also settings are now advised to pro-actively contact people if necessary, and so this may

increase resource use. The overall impact of these changes are likely to offset each other to some extent.

The changes to the recommendations on expectant management regarding the provision of pregnancy tests to women (instead of advising them to purchase them) will lead to an increase in the number of pregnancy tests supplied to women by the NHS. Pregnancy tests are inexpensive and this recommendation is not expected to have a significant resource impact to the NHS.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.11 to 1.5.19.

References – included studies

Effectiveness

Chu 2020

Chu JJ; Devall AJ; Beeson LE; Hardy P; Cheed V; Sun Y; Roberts TE; Ogwulu CO; Williams E; Jones LL; La Fontaine Papadopoulos JH; Bender-Atik R; Brewin J; Hinshaw K; Choudhary M; Ahmed A; Naftalin J; Nunes N; Oliver A; Izzat F; Bhatia K; Hassan I; Jeve Y; Hamilton J; Deb S; Bottomley C; Ross J; Watkins L; Underwood M; Cheong Y; Kumar CS; Gupta P; Small R; Pringle S; Hodge F; Shahid A; Gallos ID; Horne AW; Quenby S; Coomarasamy A; Mifepristone and misoprostol versus misoprostol alone for the management of missed miscarriage (MifeMiso): a randomised, double-blind, placebo-controlled trial.; Lancet (London, England); 2020; vol. 396 (no. 10253)

Economic

Devall A; Chu J; Beeson L; Hardy P; Cheed V; Sun Y, et al. Mifepristone and misoprostol versus placebo and misoprostol for resolution of miscarriage in women diagnosed with missed miscarriage: the MifeMiso RCT. Health Technol Assess 2021;25(68).

Other

Leveno, K.J.; Corton, M.M.; Bloom, S.L. Manual of Pregnancy Complications, 23th ed.; McGraw-Hill Medical: New York, NY, USA, 2013.

Appendices

Appendix A Review protocols

Review protocol for review question: Is the combination of mifepristone and misoprostol more effective than misoprostol alone in the medical management of missed miscarriage?

Table 4: PICO table for targeted review on medical management of miscarriage

PICO table for the review question below is based on the MifeMiso trial which was included in this targeted review. For targeted reviews only papers identified by surveillance report were included and PICO tables were drafted to retrofit to the evidence identified for the review question in the surveillance report.

Population	Inclusion: • Women diagnosed with a missed miscarriage by pelvic ultrasound scan in the first 14 weeks of pregnancy and choosing to have medical management of miscarriage. Exclusion: • Women or people experiencing miscarriage with a diagnosis of incomplete miscarriage • Women or people experiencing miscarriage opting for alternative methods of miscarriage management (expectant or surgical) • Life threatening bleeding
Intervention	Mifepristone and misoprostol in combination
Comparison	Misoprostol and placebo
Outcomes	Critical: • Failure to spontaneously pass the gestational sac within 7 days after random assignment. • Surgical intervention to complete the miscarriage up to discharge from hospital care. Important: • Surgical intervention to complete the miscarriage up to and including 7 days after random assignment. • Surgical intervention to complete the miscarriage from after day 7 and up to discharge

	• Need for further doses of misoprostol within 7 days after random assignment. • Need for further doses of misoprostol up to discharge. • Infection requiring outpatient antibiotic treatment. • Infection requiring inpatient antibiotic treatment. • Negative pregnancy test result 21 days (±2 days) after random assignment. • Duration of bleeding as reported by the participant (days). • Requirement for blood transfusion. • Side-effects. • Any serious complications. • Maternal death.
Study design	• RCTs

Appendix B Literature search strategies

Literature search strategies for review question: Is the combination of mifepristone and misoprostol more effective than misoprostol alone in the medical management of missed miscarriage?

There was no literature search conducted for this review.

Appendix C Effectiveness evidence study selection

Study selection for: Is the combination of mifepristone and misoprostol more effective than misoprostol alone in the medical management of missed miscarriage?

There was no study selection for this review: 1 study identified by surveillance was included.

Appendix D Evidence tables

Evidence tables for review question: Is the combination of mifepristone and misoprostol more effective than misoprostol alone in the medical management of missed miscarriage?

Chu, 2020

Bibliographic Reference	Chu JJ; Devall AJ; Beeson LE; Hardy P; Cheed V; Sun Y; Roberts TE; Ogwulu CO; Williams E; Jones LL; La Fontaine Papadopoulos JH; Bender-Atik R; Brewin J; Hinshaw K; Choudhary M; Ahmed A; Naftalin J; Nunes N; Oliver A; Izzat F; Bhatia K; Hassan I; Jeve Y; Hamilton J; Deb S; Bottomley C; Ross J; Watkins L; Underwood M; Cheong Y; Kumar CS; Gupta P; Small R; Pringle S; Hodge F; Shahid A; Gallos ID; Horne AW; Quenby S; Coomarasamy A; Mifepristone and misoprostol versus misoprostol alone for the management of missed miscarriage (MifeMiso): a randomised, double-blind, placebo-controlled trial.; Lancet (London, England); 2020; vol. 396 (no. 10253)

Study details

Country/ies where study was carried out	UK (Multi-Centre- 28 UK hospitals)
Study type	Randomised controlled trial (RCT)
Study dates	3 October 2017 - 22 July 2019
Inclusion criteria	• >16 years • Diagnosed with a missed miscarriage by pelvic ultrasound scan in the first 14 weeks of pregnancy (by last menstrual period) • Chose to have medical management of miscarriage • Willing and able to give informed consent
Exclusion criteria	• Expectant or surgical management of miscarriage • Had a diagnosis of incomplete miscarriage, life threatening bleeding, contraindications to mifepristone or misoprostol • Had participated in another trial of investigational medicinal products during their current pregnancy
Patient characteristics	Maternal age - years - mean ± standard deviation • Mifepristone plus misoprostol group: 32.8 ± 5.6 • Placebo plus misoprostol group: 32.7 ± 5.7 BMI - mean ± standard deviation • Mifepristone plus misoprostol group: 25.8 ± 5.6 • Placebo plus misoprostol group: 26.5 ± 5.5

	Previous parity - number (%) Mifepristone plus misoprostol group: • Nulliparous: 167 (47) • Parous: 190 (53) Placebo plus misoprostol group: • Nulliparous: 168 (47) • Parous: 186 (53) Gestational age - days - mean ± standard deviation • Mifepristone plus misoprostol group: 70.5 ± 13.1 • Placebo plus misoprostol group: 70.7 ± 13.8 Ethnicity - number (%) Mifepristone plus misoprostol group: • White: 296 (83) • Black: 10 (3) • Asian: 38 (11) • Other: 12 (3) Placebo plus misoprostol group: • White: 280 (79) • Black: 17 (5) • Asian: 42 (12) • Other: 15 (4)
Intervention(s)/control	• Single dose of oral mifepristone 200 mg and single dose of vaginal, oral, or sublingual misoprostol 800 µg 48 h later • Single dose of oral placebo tablet single dose of vaginal, oral, or sublingual misoprostol 800 µg 48 h later The single dose of misoprostol 800 µg could be omitted if the gestational sac had already been passed after the mifepristone or placebo tablet. If there was little or no bleeding within 48 hours, they were asked to contact the research team for consideration of a further dose of misoprostol. Participants were advised to return for a pelvic ultrasound scan 7 days after random assignment.

Duration of follow-up	1 month
Sources of funding	Research support grants from the Medical Research Council, National Institute for Health Research, Chief Scientist's Office, Wellbeing of Women, Roche Diagnostics, AstraZeneca, and Ferring, outside the submitted work.

Sample size	Randomised N= 711
	• Mifepristone plus misoprostol group: n = 357
	• Placebo plus misoprostol group: n = 354
	
	Excluded
	• Mifepristone plus misoprostol group: n = 8
	  ○ (5 lost to follow up, 3 discontinued study treatment and did not wish to attend follow-up or for further data to be collected)
	• Placebo plus misoprostol group: n = 5
	  ○ (2 lost to follow up, 3 discontinued study treatment and did not wish to attend follow-up or for further data to be collected)
	
	Completed 6-7 day follow up
	• Mifepristone plus misoprostol group: n = 349
	• Placebo plus misoprostol group: n = 349
	
	Excluded
	• Mifepristone plus misoprostol group: n = 1 missing primary outcome data
	• Placebo plus misoprostol group: n = 1 missing primary outcome data
	
	Included in data analysis of primary outcome
	• Mifepristone plus misoprostol group: n = 348
	• Placebo plus misoprostol group: n = 348

Other information	

Outcomes

Outcome	Mifepristone plus misoprostol group, , N = 357	Placebo plus misoprostol group, , N = 354
Failure to spontaneously pass the gestational sac within 7 days after random assignment Mifepristone plus misoprostol n= 348; Placebo plus misoprostol n= 348. Lower values are better No of events	n = 59 ; % = 17	n = 82 ; % = 24
Surgical intervention to complete the miscarriage up to discharge from hospital care Mifepristone plus misoprostol n= 355; Placebo plus misoprostol n= 353. Lower values are better No of events	n = 62 ; % = 17	n = 87 ; % = 25
Surgical intervention to complete the miscarriage up to and including day 7 after random assignment Mifepristone plus misoprostol n= 355; Placebo plus misoprostol n= 353. Lower values are better No of events	n = 23 ; % = 6.5	n = 19 ; % = 5.4
Surgical intervention to complete the miscarriage from after day 7 and up to discharge from hospital care Mifepristone plus misoprostol n= 355; Placebo plus misoprostol n= 353. Lower values are better No of events	n = 39 ; % = 11	n = 68 ; % = 19
Need for further doses of misoprostol within 7 days after random assignment Mifepristone plus misoprostol n= 356; Placebo plus misoprostol n= 354. Lower values are better No of events	n = 34 ; % = 10	n = 48 ; % = 14

Outcome	Mifepristone plus misoprostol group, , N = 357	Placebo plus misoprostol group, , N = 354
Need for further doses of misoprostol up to discharge Mifepristone plus misoprostol n= 357; Placebo plus misoprostol n= 354. Lower values are better No of events	n = 50 ; % = 14	n = 65 ; % = 18
Infection requiring outpatient antibiotic treatment Mifepristone plus misoprostol n= 351; Placebo plus misoprostol n= 351. Lower values are better No of events	n = 8 ; % = 2	n = 11 ; % = 3
Infection requiring inpatient antibiotic treatment Mifepristone plus misoprostol n= 351; Placebo plus misoprostol n= 351. Lower values are better No of events	n = 5 ; % = 1	n = 4 ; % = 1
Negative pregnancy test result 21 days (±2 days) after random assignment Mifepristone plus misoprostol n= 308; Placebo plus misoprostol n= 302. Higher values are better No of events	n = 237 ; % = 77	n = 230 ; % = 76
Duration of bleeding reported by woman, days Mifepristone plus misoprostol n= 326; Placebo plus misoprostol n= 330. Lower values are better Mean (SD)	16 (12.6)	16.3 (15.2)
Requirement for blood transfusion Mifepristone plus misoprostol n= 357; Placebo plus misoprostol n= 351. Lower values are better	n = 11 ; % = 3	n = 5 ; % = 1

Outcome	Mifepristone plus misoprostol group, , N = 357	Placebo plus misoprostol group, , N = 354
No of events		
Serious adverse event Women experiencing at least one serious adverse event. Collected up to discharge. Mifepristone plus misoprostol n= 357; Placebo plus misoprostol n= 354. Lower values are better **No of events**	n = 5 ; % = 1	n = 2 ; % = 1
Side effects Reported as 'adverse side effects'. Mifepristone plus misoprostol n= 357; Placebo plus misoprostol n= 354. Collected up to discharge; Total number of women experiencing at least one adverse side effect. Lower values are better No of events	n = 26 ; % = 7	n = 24 ; % = 7
Maternal death Mifepristone plus misoprostol n= 357; Placebo plus misoprostol n= 354. Lower values are better No of events	n = 0 ; % = 0	n = 0 ; % = 0

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Participants were randomly assigned 1:1 by a secure web-based randomisation program provided by MedSciNet. Participants, clinicians, pharmacists, trial nurses, and midwives were masked to study group*

Section	Question	Answer
		assignment throughout the trial. No differences in participant characteristic at baseline.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, clinicians, pharmacists, trial nurses, and midwives were masked to study group assignment throughout the trial. Intention to treat analysis followed and all analyses were prespecified in a statistical analysis plan.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *[Outcome data available for most participants for all outcomes. (Failure to spontaneously pass the gestational sac within 7 days after random assignment; Surgical intervention to complete the miscarriage up to discharge from hospital care; Surgical intervention to complete the miscarriage up to and including 7 days after random assignment; Surgical intervention to complete the miscarriage from after day 7 and up to discharge; Need for further doses of misoprostol within 7 days after random assignment; Need for further doses of misoprostol up to discharge; Infection requiring outpatient antibiotic treatment; Infection requiring inpatient antibiotic treatment; Negative pregnancy test result 21 days (±2 days) after random assignment; Duration of bleeding as reported by the participant (days); Requirement for blood transfusion; Side-effects; Serious adverse events; Maternal death). Missing data stated to be less than 3%.]*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Double blind trial so participants, clinicians, pharmacists, trial nurses, and midwives were blinded.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(A pre-specified protocol was available to assess selective reporting.)*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation across outcomes

RoB: risk of bias

Appendix E Forest plots

Forest plots for review question: Is the combination of mifepristone and misoprostol more effective than misoprostol alone in the medical management of missed miscarriage?

No meta-analysis was conducted for this review question and so there are no forest plots.

Appendix F GRADE tables

GRADE tables for review question: Is the combination of mifepristone and misoprostol more effective than misoprostol alone in the medical management of missed miscarriage?

Table 5: Evidence profile for comparison 1: 200mg mifepristone and 800 microgram misoprostol versus placebo and 800 microgram misoprostol

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	200mg Mifepristone and 800ug misoprostol	200mg Placebo and 800ug misoprostol	Relative (95% CI)	Absolute		
Failure to spontaneously pass the gestational sac within 7 days after random assignment (follow up at 7 days)												
Chu, 2020	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	59/348 (17%)	82/348 (23.6%)	RR 0.72 (0.53 to 0.97)	66 fewer per 1000 (from 7 fewer to 111 fewer)	MODERATE	CRITICAL
Surgical intervention to complete the miscarriage up to discharge from hospital care (follow up at 7 days)												
Chu, 2020	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	62/355 (17.5%)	87/353 (24.6%)	RR 0.71 (0.53 to 0.95)	71 fewer per 1000 (from 12 fewer to 116 fewer)	MODERATE	CRITICAL
Surgical intervention to complete the miscarriage up to and including day 7 after random assignment (follow up at 7 days)												
Chu, 2020	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	23/355 (6.5%)	19/353 (5.4%)	RR 1.2 (0.67 to 2.17)	11 more per 1000 (from 18 fewer to 63 more)	LOW	IMPORTANT
Surgical intervention to complete the miscarriage from after day 7 and up to discharge from hospital care (follow up at 7 days)												

Chu, 2020	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	39/355 (11%)	68/353 (19.3%)	RR 0.57 (0.4 to 0.82)	83 fewer per 1000 (from 35 fewer to 116 fewer)	MODERATE	IMPORTANT
Need for further doses of misoprostol within 7 days after random assignment (follow up at 7 days)												
Chu, 2020	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	34/356 (9.6%)	48/354 (13.6%)	RR 0.7 (0.47 to 1.07)	41 fewer per 1000 (from 72 fewer to 9 more)	MODERATE	IMPORTANT
Need for further doses of misoprostol up to discharge (follow up at 7 days)												
Chu, 2020	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	50/357 (14%)	65/354 (18.4%)	RR 0.76 (0.54 to 1.07)	44 fewer per 1000 (from 84 fewer to 13 more)	MODERATE	IMPORTANT
Infection requiring outpatient antibiotic treatment (follow up unclear)												
Chu, 2020	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	8/351 (2.3%)	11/351 (3.1%)	RR 0.73 (0.3 to 1.79)	8 fewer per 1000 (from 22 fewer to 25 more)	LOW	IMPORTANT
Infection requiring inpatient antibiotic treatment (follow up unclear)												
Chu, 2020	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	5/351 (1.4%)	4/351 (1.1%)	RR 1.25 (0.34 to 4.62)	3 more per 1000 (from 8 fewer to 41 more)	LOW	IMPORTANT
Negative pregnancy test result 21 days (± 2 days) after random assignment [follow up 21 days (± 2 days)]												
Chu, 2020	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	237/308 (76.9%)	230/302 (76.2%)	RR 1.01 (0.93 to 1.1)	8 more per 1000 (from 53 fewer to 76 more)	HIGH	IMPORTANT
Duration of bleeding reported by woman (days) (follow up unclear)												

Chu, 2020	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	326	330	-	MD 0.3 lower (2.44 lower to 1.84 higher)[3]	HIGH	IMPORTANT
Requirement for blood transfusion (follow up unclear)												
Chu, 2020	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	11/357 (3.1%)	5/351 (1.4%)	RR 2.16 (0.76 to 6.16)	17 more per 1000 (from 3 fewer to 74 more)	LOW	IMPORTANT
Serious adverse event[a] (follow up unclear)												
Chu, 2020	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	5/357 (1.4%)	2/354 (0.56%)	RR 2.48 (0.48 to 12.69)	8 more per 1000 (from 3 fewer to 66 more)	LOW	IMPORTANT
Side effects (follow up unclear)												
Chu, 2020	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	26/357 (7.3%)	24/354 (6.8%)	RR 1.07 (0.63 to 1.83)	5 more per 1000 (from 25 fewer to 56 more)	LOW	IMPORTANT
Maternal death[b] (follow up unclear)												
Chu, 2020	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/357 (0%)	0/354 (0%)	RD 0 (-0.01 to 0.01)	0 fewer per 1000 (from 10 fewer to 10 more)	HIGH	IMPORTANT

RR: risk ratio, RD: risk difference; MD: mean difference

[a] No details of adverse and serious events were reported in the paper
[b] Risk difference used as there were zero events in both arms.
[1] 95% CI crosses 1 MID (0.8)
[2] 95% CI crosses 2 MIDs (0.8 and 1.25)
[3] MID (0.5x control group SD, for duration of bleeding reported by woman = 7.6)

Appendix G Economic evidence study selection

Study selection for: Is the combination of mifepristone and misoprostol more effective than misoprostol alone in the medical management of missed miscarriage?

There was no study selection for this review: 1 study identified by surveillance was included.

Appendix I Economic evidence tables

Economic evidence tables for review question: Is the combination of mifepristone and misoprostol more effective than misoprostol alone in the medical management of missed miscarriage?

Table 6: Economic evidence tables for

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Author and year: Devall 2021 **Country:** UK **Type of economic analysis:** Cost utility analysis **Source of funding:** Heath Technology Assessment programme of the National Institute for Health Research	**Intervention in detail:** 357 women attending EPUs in secondary or tertiary care NHS hospitals randomised to 200mg oral mifepristone plus 800 microgram misoprostol. **Comparator** 354 women attending EPUs in secondary or tertiary care NHS hospitals randomised to Oral placebo plus 800microgram misoprostol.	**Population characteristics:** Women aged ≥16 years opting for medical management of a missed miscarriage. **Modelling approach/alongside an RCT:** Economic evaluation alongside an RCT **Source of baseline data:** Control group of RCT **Source of effectiveness data:** Intervention arm in RCT **Source of cost data:**	**Mean cost per participant:** *Intervention:* £621 *Control:* £803 *Difference:* -£182 **Primary measure of outcome:** QALYs Quality of life was estimated using EQ-5D-5L questionnaires **Mean outcome per participant:** *Intervention:* 0.0324 QALYs	**ICERs:** Mifepristone plus misoprostol dominates **Probability of being cost effective:** >50% Sensitivity analysis: Mifepristone and misoprostol remained less costly and more effective than misoprostol plus placebo for all the following scenarios: • Different cost for vaginal administration of extra dose of misoprostol • Removing costs for additional dose of misoprostol	**Perspective:** NHS and a Personal Social Services perspective **Currency:** GBP **Cost year:** 2019-20 **Time horizon:** 21 days post randomisation **Discounting:** N/A **Applicability:** Directly applicable **Limitations:**

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		Resource use data was collected as part of the trial. **Source of unit cost data:** BNF 2019, PSSRU 2002, NHS Reference Costs 2018-19.	*Control:* 0.0319 QALYs *Difference:* 0.0004	• Removal of costs of surgery • Imputation of hospital care costs	Minor limitations

BNF = British National Formulary; EPU = Early Pregnancy Unit; GBP = Great British Pound;; ICER = Incremental cost-effectiveness ratio; PSSRU = Personal and Social Services Research Unit; QALYs = Quality adjusted life years; RCT = Randomised control trial;

Appendix J Economic model

Economic model for review question: Is the combination of mifepristone and misoprostol more effective than misoprostol alone in the medical management of missed miscarriage?

No economic analysis was conducted for this review question.

Appendix K Excluded studies

Excluded studies for review question: Is the combination of mifepristone and misoprostol more effective than misoprostol alone in the medical management of missed miscarriage?

Excluded effectiveness studies

There was no literature search done for this review therefore there are no excluded studies.

Excluded economic studies

There was no literature search done for this review therefore there are no excluded studies.

Appendix L Research recommendations – full details

Research recommendations for review question: Is the combination of mifepristone and misoprostol more effective than misoprostol alone in the medical management of missed miscarriage?

No research recommendations were made for this review question.