National Institute for Health and Care Excellence

Draft for consultation

Termination of Pregnancy

[J] Misoprostol after mifepristone for inducing medical termination of pregnancy between 10^{+1} to 24^{+0} weeks' gestation

NICE guideline <TBC>

Evidence reviews

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Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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ISBN:

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Misoprostol after mifepristone for inducing medical termination of pregnancy between 10^{+1} to 24^{+0} weeks' gestation

Review question

What is the optimal regimen and route of administration of misoprostol after mifepristone, for inducing medical termination from 10^{+1} to 24^{+0} weeks?

Introduction

The aim of this review is to determine the optimal regimen and route of administration for misoprostol (after mifepristone) between 10^{+1} and 24^{+0} weeks' gestation.

PICO table

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 who are having a medical termination of pregnancy between 10^{+0} and 24^{+0} weeks' gestation
Intervention	Route of misoprostol administration: • Vaginal • Oral • Sublingual • Buccal Dose of misoprostol: • 200 micrograms (mcg) • 400 mcg • 600 mcg • 800 mcg Dose interval
Comparison	All combinations of the routes of administration, doses, number of doses, and dosing intervals listed above will be compared.
Outcome	**Critical outcomes:** • Time to expulsion • Complete abortion without the need for surgical intervention • Incomplete abortion with the need for surgical intervention **Important outcomes:** • Haemorrhage requiring transfusion or >500 ml of blood loss • Vomiting • Patient satisfaction • Diarrhoea

mcg:micrograms

Clinical evidence

Included studies

Only studies conducted from 1985 onwards were considered for this review question, as mifepristone was made available in the UK in 1991 and evidence to support the use of mifepristone in practice was unlikely to be more than 5 years before its licensing in 1991.

Eleven randomised controlled trials (RCTs; number of participants, n=1,951) were included in the review (Abbas 2016; Brouns 2010; Chai 2009; Dickinson 2014; El-Refaey 1995; Hamoda 2005; Ho 1997; Hou 2010; Mentula 2011; Ngai 2000; Tang 2005).

Four RCTs (Abbas 2016; Chai 2009; Hou 2010; Mentula 2011) compared mifepristone-misoprostol dosing intervals (simultaneous versus 24 hours, simultaneous versus 36 to 38 hours, 24 hours versus 48 hours); 6 RCTs (Dickinson 2014; El-Rafaey 1995; Hamoda 2005; Ho 1997; Ngai 2000; Tang 2005) compared 2 or more different misoprostol routes of administration (oral versus vaginal, sublingual versus vaginal, oral versus sublingual versus vaginal) and 1 RCT (Brouns 2010) compared 2 different doses of misoprostol (400 micrograms versus 200 micrograms).

There was no subgroup data available based on medical conditions, gestational age, parity and history of previous caesarean section.

The included studies are summarised in Table 2.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

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

Table 2: Summary of included studies

Study and setting	Population	Intervention/ comparison	Outcomes
Abbas 2016 RCT Vietnam	n=505 Women with a live foetus eligible for medical termination of pregnancy, with closed cervical os, no vaginal bleeding and no contraindications to study drugs 13 to 22 weeks' gestation	**Simultaneous administration of mifepristone and misoprostol:** Placebo followed 24 hours later by 200 mg mifepristone and 400 mcg buccal misoprostol followed by 400 mcg buccal misoprostol every 3 hours until expulsion of foetus or 48 hours **24 hour interval between mifepristone and misoprostol:**	• Time to expulsion • Complete abortion without the need for surgical intervention • Incomplete abortion with the need for surgical intervention • Haemorrhage requiring transfusion or >500 ml of blood loss • Vomiting • Patient satisfaction • Diarrhoea

Study and setting	Population	Intervention/ comparison	Outcomes
		200 mg mifepristone followed 24 hours later by 200 mg placebo and 400 mcg buccal misoprostol followed by 400 mcg buccal misoprostol every 3 hours until expulsion of foetus or 48 hours	
Brouns 2010 RCT The Netherlands	n =176 Women requesting termination of pregnancy 14 to 24 weeks' gestation	**200 mcg vaginal misoprostol:** 200 mcg vaginal misoprostol at 4 hour intervals, 36 to 48 hours following oral mifepristone 200 mg **400 mcg vaginal misoprostol:** 400 mcg vaginal misoprostol at 4 hour intervals, 36 to 48 hours following oral mifepristone 200 mg	• Time to expulsion • Complete abortion without the need for surgical intervention • Incomplete abortion with the need for surgical intervention • Haemorrhage requiring transfusion or >500 ml of blood loss • Vomiting • Diarrhoea
Chai 2009 RCT China	n=141 Healthy women, more than 18 years old, requesting termination of pregnancy and willing to comply with follow to up 12 to 20 weeks' gestation	**Simultaneous administration of mifepristone and misoprostol:** 200 mg mifepristone orally followed by 600 mcg vaginal misoprostol immediately, which was then followed by 400 mcg vaginal misoprostol every 3 hours up to 4 doses **36 to 38 hour interval between mifepristone and misoprostol:** 200 mg mifepristone orally followed by 600 mcg vaginal misoprostol 36 to 38 hours later followed by 400 mcg vaginal misoprostol every 3 hours up to 4 doses	• Time to expulsion • Complete abortion without the need for surgical intervention • Incomplete abortion with the need for surgical intervention • Haemorrhage requiring transfusion or >500 ml of blood loss • Diarrhoea
Dickinson 2014 RCT Australia	n=302 Women requesting a second trimester medical abortion for foetal abnormality or maternal medical complication	**Oral misoprostol:** mifepristone 200 mg followed 24 to 48 hours later by 800 mcg vaginal misoprostol followed by 400 mcg oral misoprostol every 3 hours up to 5 doses **Vaginal misoprostol:**	• Time to expulsion • Complete abortion without the need for surgical intervention • Haemorrhage requiring transfusion or >500 ml of blood loss • Patient satisfaction

Study and setting	Population	Intervention/ comparison	Outcomes
	14 to 24 weeks' gestation	mifepristone 200 mg followed 24 to 48 hours later by 800 mcg vaginal misoprostol followed by 400 mcg vaginal misoprostol every 4 hours up to 5 doses **Sublingual misoprostol:** mifepristone 200 mg followed 24 to 48 hours later by 800 mcg vaginal misoprostol followed by 400 mcg sublingual misoprostol every 3 hours up to 5 doses	
El-Refaey 1995 RCT United Kingdom	n=69 Women requesting termination of pregnancy for socioeconomic reasons 13 to 20 weeks' gestation	**Vaginal misoprostol:** 600 mg mifepristone orally followed by 600 mcg vaginal misoprostol 36 to 48 hours later and then misoprostol 400 mcg vaginal every 3 hours up to 4 doses. **Oral misoprostol:** 600 mg mifepristone orally followed by 600 mcg vaginal misoprostol 36 to 48 hours later and then 400 mcg oral misoprostol every 3 hours up to 4 doses.	• Time to expulsion • Complete abortion without the need for surgical intervention • Haemorrhage requiring transfusion or >500 ml of blood loss • Vomiting • Diarrhoea
Hamoda 2005 RCT United Kingdom	n=76 Women with viable singleton pregnancies requesting for medical termination of pregnancy 13 to 20 weeks' gestation	**Sublingual misoprostol:** 200 mg mifepristone followed 36 to 48 hours later by 600 mcg sublingual misoprostol. Further 3 hourly doses of 400 mcg sublingual misoprostol up to 5 doses **Vaginal misoprostol:** 200 mg mifepristone followed 36 to 48 hours later by vaginal misoprostol 800 mcg. Further 3 hourly doses of 400 mcg vaginal misoprostol up to 5 doses	• Time to expulsion • Incomplete abortion with the need for surgical intervention • Vomiting • Patient satisfaction • Diarrhoea
Ho 1997 RCT China	n=98 Healthy women aged 16 to 35 years with	**Oral misoprostol:** 200 mg mifepristone followed 36 to 48 hours later by 200 mcg oral misoprostol and vaginal	• Time to expulsion • Complete abortion without the need for surgical intervention

Study and setting	Population	Intervention/ comparison	Outcomes
	singleton pregnancy 14 to 20 weeks' gestation	placebo every 3 hours up to 5 doses **Vaginal misoprostol:** 200 mg mifepristone followed 36 to 48 hours later by 200 mcg misoprostol vaginally and a placebo orally every 3 hours up to 5 doses	• Incomplete abortion with the need for surgical intervention • Vomiting • Diarrhoea
Hou 2010 RCT China	n=100 Healthy women aged 18 to 45 years requesting termination of pregnancy and willing to comply with follow-up visits 13 to 16 weeks' gestation	**1 day interval**: 200 mg oral mifepristone followed 1 day later by 600 mcg vaginal misoprostol and 400 mcg oral misoprostol every 6 hours up to 2 doses **2 day interval**: 200 mg oral mifepristone followed 2 days later by 600 mcg vaginal misoprostol and 400 mcg oral misoprostol every 6 hours up to 2 doses	• Time to expulsion • Complete abortion without the need for surgical intervention • Incomplete abortion with the need for surgical intervention • Vomiting • Diarrhoea
Mentula 2011 RCT Finland	n=227 Women more than 18 years age, with a viable singleton pregnancy and a legal indication for termination of pregnancy	**1 day interval**: 200 mg mifepristone oral followed by 400 mcg vaginal misoprostol 20 to 28 hours later and then every 3 hours, for up to 5 doses per 24 hours **2 day interval:** 200 mg mifepristone orally followed by 400 mcg vaginal misoprostol 2 days (40 to 48 hours) later and every 3 hours with up to 5 doses per 24 hours	• Time to expulsion • Incomplete abortion with the need for surgical intervention • Haemorrhage requiring transfusion or >500 ml of blood loss • Vomiting
Ngai 2000 RCT China	n=139 Healthy women aged 16 to 35 years requesting legal termination of pregnancy 14 to 20 weeks' gestation	**Oral misoprostol 400 mcg:** 200 mg mifepristone oral followed 36 to 48 hours later by 400 mcg oral misoprostol every 3 hours up to 5 doses + vaginal vitamin B6 placebo **Vaginal misoprostol 200 mcg:** 200 mg mifepristone oral followed 36 to 48 hours later by 200 mcg vaginal misoprostol every 3 hours up to 5 doses + oral vitamin B6 placebo	• Time to expulsion • Complete abortion without the need for surgical intervention • Incomplete abortion with the need for surgical intervention • Vomiting • Diarrhoea

Study and setting	Population	Intervention/ comparison	Outcomes
Tang 2005 RCT China	n=118 Women more than 18 years old, requesting a legal termination of pregnancy 12 to 20 weeks' gestation	**Sublingual misoprostol**: 200 mg mifepristone oral followed 36 to 48 hours later by sublingual misoprostol 400 mcg every 3 hours up to 5 doses **Oral misoprostol**: 200 mg oral mifepristone followed 36 to 48 hours later by oral misoprostol 400 mcg every 3 hours up to 5 doses	• Time to expulsion • Complete abortion without the need for surgical intervention • Incomplete abortion with the need for surgical intervention • Diarrhoea

mcg: micrograms; RCT: randomised controlled trial

See the full evidence tables in appendix D and the forest plots in appendix E.

Quality assessment of clinical studies included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

A single economic search was undertaken for all topics included in the scope of this guideline. See supplementary material 2 for details.

Excluded studies

No full-text copies of articles were requested for this review and so there is no excluded studies list.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

Comparison 1. 200 mcg versus 400 mcg vaginal misoprostol (at 4 hour intervals) 36 to 48 hours after oral mifepristone 200 mg

Critical outcomes

Time to expulsion

RCT evidence showed that the time to expulsion was statistically[a] significantly longer in the 200 mcg vaginal misoprostol group (median [range]=9.2 [7.1 to 11.3] hours) compared with

[a] Due to the use of medians for which there are no established or default GRADE MIDs it is unclear whether these differences are clinically important.

the 400 mcg vaginal misoprostol group (median [range]=8.0 [7.1 to 8.9] hours; 1 RCT, n=176; low quality)

Complete abortion without the need for surgical intervention

RCT evidence did not detect a clinically important difference in complete abortion rate without the need for surgical intervention (at 48 hours) between the 200 mcg vaginal misoprostol group and the 400 mcg vaginal misoprostol group (1 RCT, n=176; RR=0.9 [95% CI 0.74, 1.10]; low quality); however, there was uncertainty around the estimate.

Incomplete abortion with the need for surgical intervention

RCT evidence did not detect a clinically important difference in the incomplete abortion rate with the need for surgical intervention between the 200 mcg vaginal misoprostol group and the 400 mcg vaginal misoprostol group (1 RCT, n=176; RR=1.26 [95% CI 0.80, 1.99]; low quality); however, there was uncertainty around the estimate..

Important outcomes

Haemorrhage requiring transfusion or >500 ml of blood loss

RCT evidence did not detect a clinically important difference in the rate of haemorrhage requiring transfusion or >500 ml of blood loss between the 200 mcg vaginal misoprostol group and the given 400 mcg vaginal misoprostol group (1 RCT, n=176; RR=1.4 [95% CI 0.32, 6.05]; low quality); however, there was uncertainty around the estimate..

Vomiting

RCT evidence did not detect a clinically important difference in the rate of vomiting between the 200 mcg vaginal misoprostol group and the 400 mcg vaginal misoprostol group (1 RCT, n=176; RR=0.76 [95% CI 0.51, 1.14]; moderate quality); however, there was uncertainty around the estimate..

Patient satisfaction

No evidence was identified to inform this outcome.

Diarrhoea

RCT evidence did not detect a clinically important difference in the rate of diarrhoea between the 200 mcg vaginal misoprostol group and the 400 mcg vaginal misoprostol group (1 RCT, n=176; RR=0.52 [95% CI 0.19, 1.47]; low quality); however, there was uncertainty around the estimate.

Comparison 2. Vaginal versus oral misoprostol (400 mcg, at 3 hour intervals up to 4 doses following a loading dose of vaginal misoprostol 600 mcg) 36 to 48 hours after oral mifepristone 600 mg

Critical outcomes

Time to expulsion

RCT evidence showed there was no clinically important difference in the time to expulsion between the 400 mcg vaginal misoprostol group and the 400 mcg oral misoprostol group (1 RCT, n=69; MD= -0.7 [95% CI -2.03, 0.63]; high quality)

Complete abortion without the need for surgical intervention

RCT evidence did not a detect a clinically important difference in the complete abortion rate without the need for surgical intervention (at 48 hours) between the 400 mcg vaginal misoprostol group and the 400 mcg oral misoprostol group (1 RCT, n=69; RR=1.0 [95% CI 0.92, 1.09]; low quality); however, there was uncertainty around the estimate.

Incomplete abortion with the need for surgical intervention

RCT evidence did not a detect a clinically important difference in the incomplete abortion rate with the need for surgical intervention between the 400 mcg vaginal misoprostol group and the 400 mcg oral misoprostol group (1 RCT, n=69; RR=3.09 [95% CI 0.13, 73.21]; low quality); however, there was uncertainty around the estimate.

Important outcomes

Haemorrhage requiring transfusion or >500ml of blood loss

RCT evidence reported no events of haemorrhage requiring transfusion or >500 ml of blood loss in either the 400 mcg vaginal misoprostol group or the 400 mcg oral misoprostol group; therefore differences between groups could not be estimated (1 RCT, n=69;low quality).

Vomiting

RCT evidence did not detect a clinically important difference in the rate of vomiting between the 400 mcg vaginal misoprostol group and the 400 mcg oral misoprostol group (1 RCT, n=69; RR=0.93 [95% CI 0.63, 1.37]; low quality); however, there was uncertainty around the estimate..

Patient satisfaction

No evidence was identified to inform this outcome.

Diarrhoea

RCT evidence did not detect a clinically important difference in the rate of diarrhoea between the 400 mcg vaginal misoprostol group and the 400 mcg oral misoprostol group (1 RCT, n=69; RR=0.81 [95% CI 0.40, 1.62]; low quality); however, there was uncertainty around the estimate..

Comparison 3. Vaginal versus oral misoprostol (400 mcg; at 4 hour intervals for vaginal misoprostol and 3 hour intervals for oral misoprostol, up to 5 doses following a loading dose of vaginal misoprostol 800 mcg) 24 to 48 hours after oral mifepristone 200 mg

Critical outcomes

Time to expulsion

RCT evidence showed that the time to expulsion was statistically[b] significantly shorter in the 400 mcg vaginal misoprostol group (median [range]=7.4 [6.5 to 8.2] hours) compared with the 400 mcg oral misoprostol group (median [range]=9.5 (8.5 to 11.4) hours; 1 RCT, n=200; moderate quality).

[b] Due to the use of medians for which there are no established or default GRADE MIDs it is unclear whether these differences are clinically important.

Complete abortion without the need for surgical intervention

No evidence was identified to inform this outcome.

Incomplete abortion with the need for surgical intervention

No evidence was identified to inform this outcome.

Important outcomes

Haemorrhage requiring transfusion or >500ml of blood loss

RCT evidence did not detect a clinically important difference in the rate of haemorrhage requiring transfusion or >500 ml of blood loss between the 400 mcg vaginal misoprostol group and the 400 mcg oral misoprostol group (1 RCT, n=200; RR=0.50 [95% CI 0.05, 5.43]; low quality); however, there was uncertainty around the estimate.

Vomiting

No evidence was identified to inform this outcome.

Patient satisfaction (opinion of procedure score)

RCT evidence did not detect a clinically important difference in the opinion of procedure (with lower scores indicating “better than expected” and higher scores indicating “worse than expected”) patient satisfaction score between the 400 mcg vaginal misoprostol group (median [range]=50 [26 to 50]) and the 400 mcg oral misoprostol group (median [range]=50 [20 to 50]; 1 RCT, n=200; low quality); however, there was uncertainty around the estimate.

Diarrhoea

No evidence was identified to inform this outcome.

Comparison 4. Vaginal versus oral misoprostol (200 mcg; at 3 hour intervals, up to 5 doses) ± placebo 36 to 48 hours after 200 mg oral mifepristone

Critical outcomes

Time to expulsion

RCT evidence showed a shorter clinically important difference in the time to expulsion in the 200 mcg vaginal misoprostol group compared with the 200 mcg oral misoprostol group (1 RCT, n=98; MD=-13 [95% CI -23.23, -2.77]; low quality).

Complete abortion without the need for surgical intervention

RCT evidence did not detect a clinically important difference in the complete abortion rate without the need for surgical intervention (at 48 hours) between the 200 mcg vaginal misoprostol group and the 200 mcg oral misoprostol group (1 RCT, n=98; RR=1.24 [95% CI 0.93, 1.65]; low quality); however, there was uncertainty around the estimate.

Incomplete abortion with the need for surgical intervention

No evidence was identified to inform this outcome.

Important outcomes

Haemorrhage requiring transfusion or >500ml of blood loss

No evidence was identified to inform this outcome.

Vomiting

RCT evidence did not detect a clinically important difference in the rate of vomiting between the 200 mcg vaginal misoprostol group and the 200 mcg oral misoprostol group (1 RCT, n=98; RR=1.40 [95% CI 0.69, 2.84]; low quality); however, there was uncertainty around the estimate.

Patient satisfaction

No evidence was identified to inform this outcome.

Diarrhoea

RCT evidence did not detect a clinically important difference in the rate of diarrhoea between the 200 mcg vaginal misoprostol group and the 200 mcg oral misoprostol group (1 RCT, n=98; RR=0.56 [95% CI 0.28, 1.15]; moderate quality); however, there was uncertainty around the estimate.

Comparison 5. Oral versus vaginal misoprostol (400 mcg at 3 hour intervals, up to 5 doses) ± placebo 36 to 48 hours after oral mifepristone 200 mg

Critical outcomes

Time to expulsion

RCT evidence showed there was no clinically important difference in the time to expulsion between the 400 mcg oral misoprostol group and the 400 mcg vaginal misoprostol group (1 RCT, n=139; MD=-1.3 [95% CI -8.7, 11.33]; moderate quality).

Complete abortion without the need for surgical intervention

RCT evidence did not detect a clinically important difference in the complete abortion rate without the need for surgical intervention (at 48 hours) between the 400 mcg oral misoprostol group and the 400 mcg vaginal misoprostol group (1 RCT, n=139; RR=0.97 [95% CI 0.83, 1.13]; very low quality); however, there was uncertainty around the estimate.

Incomplete abortion with the need for surgical intervention

RCT evidence reported no events of incomplete abortion with the need for surgical intervention in either the 400 mcg oral misoprostol group or the 400 mcg vaginal misoprostol group; therefore differences between groups could not be estimated (1 RCT, n=139; very low quality).

Important outcomes

Haemorrhage requiring transfusion or >500ml of blood loss

No evidence was identified to inform this outcome.

Vomiting

RCT evidence did not detect a clinically important difference in the rate of vomiting between the 400 mcg oral misoprostol group and the 400 mcg vaginal misoprostol group (1 RCT, n=139; RR=1.05 [95% CI 0.72, 1.54]; very low quality); however, there was uncertainty around the estimate..

Patient satisfaction

No evidence was identified to inform this outcome.

Diarrhoea

RCT evidence showed a higher clinically important difference in the rate of diarrhoea in the 400 mcg oral misoprostol group compared to the 400 mcg vaginal misoprostol group (1 RCT, n=139; RR=1.73 [95% CI 1.03, 2.89]; low quality).

Comparison 6. Sublingual versus oral misoprostol (400 mcg; at 3 hour intervals, up to 5 doses following a loading dose of vaginal misoprostol 800 mcg) 24 to 48 hours after oral mifepristone 200 mg

Critical outcomes

Time to expulsion

RCT evidence showed that the time to expulsion was statistically[c] significantly shorter in the 400 mcg sublingual misoprostol group (median [range]=7.8 [7.0 to 9.2] hours) compared with the 400 mcg oral misoprostol group (median [range]=9.5 [8.5 to 11.4] hours; 1 RCT, n=202; moderate quality).

Complete abortion without the need for surgical intervention

No evidence was identified to inform this outcome.

Incomplete abortion with the need for surgical intervention

No evidence was identified to inform this outcome.

Important outcomes

Haemorrhage requiring transfusion or >500ml of blood loss

RCT evidence did not detect a clinically important difference in the rate of haemorrhage requiring transfusion or >500 ml of blood loss between the 400 mcg sublingual misoprostol group and the 400 mcg oral misoprostol group (1 RCT, n=202; RR=0.98 [95% CI 0.14, 6.83]; low quality); however, there was uncertainty around the estimate.

Vomiting

No evidence was identified to inform this outcome.

Patient satisfaction (opinion of procedure score)

RCT evidence did not detect a clinically important difference in the opinion of procedure (with lower scores indicating “better than expected” and higher scores indicating “worse than

[c] Due to the use of medians for which there are no established or default GRADE MIDs it is unclear whether these differences are clinically important.

expected") patient satisfaction score between the 400 mcg sublingual misoprostol group (median [range]=50 [19 to 50]) and the 400 mcg oral misoprostol group (median [range]=50 [20 to 50]; 1 RCT, n=202; low quality); however, there was uncertainty around the estimate.

Diarrhoea

No evidence was identified to inform this outcome.

Comparison 7. Sublingual versus oral misoprostol (400 mcg, at 3 hour intervals up to 5 doses) 36 to 48 hours after oral mifepristone 200 mg

Critical outcomes

Time to expulsion

RCT evidence showed that the time to expulsion was statistically[d] significantly shorter in the 400 mcg sublingual misoprostol group (median [range]=5.5 [1.4 to 43.2] hours) compared with the 400 mcg oral misoprostol group (median [range]=7.5 [2.4 to 38.8] hours; 1 RCT, n=118; low quality).

Complete abortion without the need for surgical intervention

RCT evidence did not detect a clinically important difference in the complete abortion rate without the need for surgical intervention (at 48 hours) between the 400 mcg sublingual misoprostol group and the 400 mcg oral misoprostol group (1 RCT, n=118; RR=1.07 [95% CI 0.99-1.17]; moderate quality); however, there was uncertainty around the estimate.

Incomplete abortion with the need for surgical intervention

RCT evidence showed did not detect a clinically important difference in the incomplete abortion rate with the need for surgical intervention between the 400 mcg sublingual misoprostol group and the 400 mcg oral misoprostol group (1 RCT, n=118; RR=1.48 [95% CI 0.60, 3.62]; low quality); however, there was uncertainty around the estimate.

Important outcomes

Haemorrhage requiring transfusion or >500ml of blood loss

No evidence was identified to inform this outcome.

Vomiting

No evidence was identified to inform this outcome.

Patient satisfaction

No evidence was identified to inform this outcome.

Diarrhoea

RCT evidence showed did not detect a clinically important difference in the rate of diarrhoea between the 400 mcg sublingual misoprostol group and the 400 mcg oral misoprostol group (1 RCT, n=118; RR=0.64 [95% CI 0.29, 1.42]; low quality); however, there was uncertainty around the estimate.

[d] Due to the use of medians for which there are no established or default GRADE MIDs it is unclear whether these differences are clinically important.

Comparison 8. Sublingual (600 mcg; followed by 400 mcg at 3 hour intervals up to 5 doses) versus vaginal (800 mcg; followed by 400 mcg at 3 hour intervals up to 5 doses) misoprostol, 36 to 48 hours after oral mifepristone 200 mg

Critical outcomes

Time to expulsion

RCT evidence did not detect a clinically important difference in the time to expulsion between the 600 mcg sublingual misoprostol group (median [range]=5.27 [0.55 to 29.35] hours) and the 800 mcg vaginal misoprostol group (median [range]=5.40 [2.10 to 13.00] hours; 1 RCT, n=76; low quality); however, there was uncertainty around the estimate.

Complete abortion without the need for surgical intervention

No evidence was identified to inform this outcome.

Incomplete abortion with the need for surgical intervention

RCT evidence did not detect a clinically important difference in the rate of incomplete abortion with the need for surgical intervention between the 600 mcg sublingual misoprostol group and the 800 mcg vaginal misoprostol group (1 RCT, n=76; RR=3.33 [95% CI 0.36, 30.63]; low quality); however, there was uncertainty around the estimate.

Important outcomes

Haemorrhage requiring transfusion or >500ml of blood loss

No evidence was identified to inform this outcome.

Vomiting

RCT evidence did not detect a clinically important difference in the rate of vomiting between the 600 mcg sublingual misoprostol group and the 800 mcg vaginal misoprostol group (1 RCT, n=76; RR=1.11 [95% CI 0.80, 1.54]; low quality); however, there was uncertainty around the estimate.

Patient satisfaction (satisfied with the route of administration)

RCT evidence did not detect a clinically important difference in the rate of women who were "satisfied" with the route of administration of misoprostol between the 600 mcg sublingual misoprostol group and the 800 mcg vaginal misoprostol group (1 RCT, n=76; RR=1.07 [95% CI 0.76, 1.49]; very low quality); however, there was uncertainty around the estimate.

Diarrhoea

RCT evidence did not detect a clinically important difference in the rate of diarrhoea between the 600 mcg sublingual misoprostol group and the 800 mcg vaginal misoprostol group (1 RCT, n=76; RR=1.01 [95% CI 0.66, 1.54]; low quality); however, there was uncertainty around the estimate.

Comparison 9. Oral misoprostol (400 mcg; every 6 hours, up to 2 doses) 1 versus 2 days after oral mifepristone 200 mg + 600 mcg vaginal misoprostol

Critical outcomes

Time to expulsion

RCT evidence showed there was no clinically important difference in the time to expulsion between the oral misoprostol 1 day after oral mifepristone group and the oral misoprostol 2 days after oral mifepristone group (1 RCT, n=100; MD=0.20 [95% CI -1.25,1.65]; low quality).

Complete abortion without the need for surgical intervention

RCT evidence showed a lower clinically important difference in the rate of complete abortion without the need for surgical intervention (at 24 hours) in the oral misoprostol 1 day after oral mifepristone group compared with the oral misoprostol 2 days after oral mifepristone group (1 RCT, n=100; RR=0.68 [95% CI 0.47, 0.97]; low quality).

Incomplete abortion with the need for surgical intervention

RCT evidence did not detect a clinically important difference in the rate of incomplete abortion with the need for surgical intervention between the oral misoprostol 1 day after oral mifepristone group and the oral misoprostol 2 days after oral mifepristone group (1 RCT, n=100; RR=3 [95% CI 0.13, 71.92]; very low quality); however, there was uncertainty around the estimate..

Important outcomes

Haemorrhage requiring transfusion or >500ml of blood loss

No evidence was identified to inform this outcome.

Vomiting

RCT evidence showed no clinically important difference in the rate of vomiting between the oral misoprostol 1 day after oral mifepristone group and the oral misoprostol 2 days after oral mifepristone group (1 RCT, n=100; RR=0.93 [95% CI 0.51, 1.72]; very low quality).

Patient satisfaction

No evidence was identified to inform this outcome.

Diarrhoea

RCT evidence showed no clinically important difference in the rate of diarrhoea between the oral misoprostol 1 day after oral mifepristone group and the oral misoprostol 2 days after oral mifepristone group (1 RCT, n=100; RR=2.25 [95% CI 0.74, 6.83]; very low quality).

Comparison 10. Vaginal misoprostol (400 mcg; at 3 hour intervals, up to 5 doses per 24 hours) 1 versus 2 days after oral mifepristone 200 mg

Critical outcomes

Time to expulsion

RCT evidence showed that the time to expulsion was statistically[e] significantly longer in the 400 mcg vaginal misoprostol 1 day after oral mifepristone group (median [range]=8.5 [6.3 to 12.3)] hours) compared with the 400 mcg vaginal misoprostol 2 days after oral mifepristone group (median [range]=7.2 [5.8 to 9.2] hours; 1 RCT, n=227; moderate quality).

Complete abortion without the need for surgical intervention

No evidence was identified to inform this outcome.

Incomplete abortion with the need for surgical intervention

RCT evidence did not detect a clinically important difference in the rate of incomplete abortion with the need for surgical intervention between the 400 mcg vaginal misoprostol 1 day after oral mifepristone group and the 400 mcg vaginal misoprostol 2 days after oral mifepristone group (1 RCT, n=227; RR=0.69 [95% CI 0.46, 1.03]; moderate quality); however, there was uncertainty around the estimate.

Important outcomes

Haemorrhage requiring transfusion or >500ml of blood loss

RCT evidence did not detect a clinically important difference in the rate of haemorrhage requiring transfusion or >500 ml blood loss between the 400 mcg vaginal misoprostol 1 day after oral mifepristone group and the 400 mcg vaginal misoprostol 2 days after oral mifepristone group (1 RCT, n=227; RR=1.11 [95% CI 0.42, 2.97]; low quality); however, there was uncertainty around the estimate.

Vomiting

RCT evidence did not detect a clinically important difference in the rate of vomiting (need for anti-emetic drugs) between the 400 mcg vaginal misoprostol 1 day after oral mifepristone group and the 400 mcg vaginal misoprostol 2 days after oral mifepristone group (1 RCT, n=227; RR=1.22 [95% CI 0.76, 1.95]; very low quality); however, there was uncertainty around the estimate.

Patient satisfaction

No evidence was identified to inform this outcome.

Diarrhoea

No evidence was identified to inform this outcome.

[e] Due to the use of medians for which there are no established or default GRADE MIDs it is unclear whether these differences are clinically important.

Comparison 11. Vaginal misoprostol (600 mcg; followed by 400 mcg at 3 hour intervals, up to 4 doses) simultaneous with mifepristone 200 mg versus 36 to 38 hours after 200 mg oral mifepristone

Critical outcomes

Time to expulsion

RCT evidence showed that the time to expulsion was statistically[f] significantly longer in the 600 mcg vaginal misoprostol simultaneously with oral mifepristone group (median [range]=10.0 [3.5 to 126] hours) compared with the 600 mcg vaginal misoprostol 36 to 38 hours after oral mifepristone group (median [range]=4.9 [1.8 to 13.8] hours; 1 RCT, n=141; low quality).

Complete abortion without the need for surgical intervention

RCT evidence did not detect a clinically important difference in the rate of complete abortion without the need for surgical intervention between the 600 mcg vaginal misoprostol simultaneously with oral mifepristone group and the 600 mcg vaginal misoprostol 36 to 38 hours after oral mifepristone group (1 RCT, n=141; RR=0.99 [95% CI 0.95, 1.03]; low quality); however, there was uncertainty around the estimate.

Incomplete abortion with the need for surgical intervention

RCT evidence did not detect a clinically important difference in the rate of incomplete abortion with the need for surgical intervention between the 600 mcg vaginal misoprostol simultaneously with oral mifepristone group and the 600 mcg vaginal misoprostol 36 to 38 hours after oral mifepristone group (1 RCT, n=141; RR=4.93 [95% CI 0.59, 41.13]; low quality); however, there was uncertainty around the estimate.

Important outcomes

Haemorrhage requiring transfusion or >500ml of blood loss

RCT evidence reported no events of haemorrhage requiring transfusion or >500ml of blood loss in either the 600 mcg vaginal misoprostol simultaneously with oral mifepristone group or the 600 mcg vaginal misoprostol 36 to 38 hours after oral mifepristone group; therefore differences between groups could not be estimated (1 RCT, n=141;; low quality).

Vomiting

No evidence was identified to inform this outcome.

Patient satisfaction

No evidence was identified to inform this outcome.

Diarrhoea

RCT evidence did not detect a clinically important difference in the rate of diarrhoea (> 3 episodes) between the 600 mcg vaginal misoprostol simultaneously with oral mifepristone group and the 600 mcg vaginal misoprostol 36 to 38 hours after oral mifepristone group (1 RCT, n=141; RR=1.77 [95% CI 0.88, 3.57]; moderate quality); however, there was uncertainty around the estimate..

[f] Due to the use of medians for which there are no established or default GRADE MIDs it is unclear whether these differences are clinically important.

Comparison 12. Buccal misoprostol 400 mcg (at 3 hour intervals) ± placebo simultaneous with mifepristone 200 mg versus 1 day following oral mifepristone 200 mg

Critical outcomes

Time to expulsion

RCT evidence showed that the time to expulsion was statistically[g] significantly longer in the buccal misoprostol simultaneously with oral mifepristone group (median [range]=13.0 [4.9 to 47.8] hours) compared with the 400 mcg buccal misoprostol 1 day after oral mifepristone group (median [range]=7.7 [2.1 to 40.3] hours; 1 RCT, n=505; moderate quality).

Complete abortion without the need for surgical intervention

RCT evidence did not detect a clinically important difference in the rate of complete abortion without the need for surgical intervention at 48 hours between the 400 mcg buccal misoprostol simultaneously with oral mifepristone group and the 400 mcg buccal misoprostol 1 day after oral mifepristone group (1 RCT, n=505; RR=0.99 [95% CI 0.95, 1.02]; low quality); however, there was uncertainty around the estimate.

Incomplete abortion with the need for surgical intervention

RCT evidence did not detect a clinically important difference in the rate of incomplete abortion with the need for surgical intervention between the 400 mcg buccal misoprostol simultaneously with oral mifepristone group and the 400 mcg buccal misoprostol 1 day after oral mifepristone group (1 RCT, n=505; RR=1.98 [95% CI 0.18, 21.66]; very low quality); however, there was uncertainty around the estimate.

Important outcomes

Haemorrhage requiring transfusion or >500ml of blood loss

RCT evidence did not detect a clinically important difference in the rate of haemorrhage requiring transfusion or >500ml of blood loss between the 400 mcg buccal misoprostol simultaneously with oral mifepristone group and the 400 mcg buccal misoprostol 1 day after oral mifepristone group (1 RCT, n=505; RR=2.96 [95% CI 0.12, 72.43]; very low quality); however, there was uncertainty around the estimate.

Vomiting

RCT evidence did not detect a clinically important difference in the rate of vomiting between the 400 mcg buccal misoprostol simultaneously with oral mifepristone group and the 400 mcg buccal misoprostol 1 day after oral mifepristone group (1 RCT, n=505; RR=1.09 [95% CI 0.8, 1.49]; very low quality); however, there was uncertainty around the estimate.

Patient satisfaction (satisfied or very satisfied)

RCT evidence showed there was no clinically important difference in the rate of patient satisfaction (satisfied or very satisfied) between the 400 mcg buccal misoprostol simultaneously with oral mifepristone group and the 400 mcg buccal misoprostol 1 day after oral mifepristone group (1 RCT, n=505; RR=1 [95% CI 0.98, 1.02]; moderate quality).

[g] Due to the use of medians for which there are no established or default GRADE MIDs it is unclear whether these differences are clinically important.

Diarrhoea

RCT evidence showed there was a higher clinically important difference in the rate of diarrhoea in the 400 mcg buccal misoprostol simultaneously with oral mifepristone group compared to the 400 mcg buccal misoprostol 1 day after oral mifepristone group (1 RCT, n=505; RR=1.63 [95% CI 1.32, 2.01]; moderate quality).

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The main aim of this review was to determine the optimal dose regimen and route of administration of misoprostol, following mifepristone for the medical termination of pregnancy between 10^{+1} and 24^{+0} weeks. The committee agreed that, the time to expulsion should be prioritised as a critical outcome as it varies with the dose regimen, the route of administration and the dosing interval of misoprostol and was critical for decision making given its implications for the woman and the health care resources. Complete abortion without the need for surgical intervention and incomplete abortion with the need for surgical intervention were selected as critical outcomes as they may have implications for the woman in terms of having to undergo surgical intervention and also impact resources. Haemorrhage requiring transfusion of greater than 500 ml of blood loss was considered an important outcome for decision making, because of the seriousness of the outcome. Patient satisfaction was considered as an important outcome as termination of pregnancy is an area where women are known to have strong preferences. Vomiting and diarrhoea were included as important outcomes to allow for a balance of the benefits and harms as the likelihood of these occurring differs with the dose regimens, routes of administration and dosing intervals of misoprostol and they are likely to impact patient satisfaction.

The quality of the evidence

The evidence in the pairwise comparisons was assessed using the GRADE methodology. Evidence for time to expulsion ranged from low to high quality; the main reason evidence was downgraded was for imprecision caused by few events of interest but there was also risk of bias due to unclear randomization and unclear allocation concealment methods. Evidence for complete abortion without the need for surgical intervention ranged from very low to moderate quality; the main reason evidence was downgraded was due to imprecision caused by 95% confidence intervals crossing minimally important difference (MID) values and risk of bias caused by inadequate information regarding randomization and allocation concealment for studies comparing misoprostol regimens. The evidence for rate of incomplete abortion with the need for surgical intervention was very low to moderate quality. As with complete abortion rate, the reasons to downgrade the evidence was imprecision and risk of bias in studies reporting this outcome. The evidence for the outcome, haemorrhage requiring transfusion or >500 ml of blood loss was very low to low quality. The reasons for downgrading of evidence were imprecision caused by a small number or no events of interest and risk of bias in the included studies due to unclear randomization methods. Evidence for vomiting and diarrhoea ranged from very low to moderate quality; the most common reasons for downgrading evidence was imprecision due to wide confidence intervals and risk of bias due to attrition and insufficient information about randomization and allocation concealment methods. Evidence for patient satisfaction was of very low to moderate quality, mainly due to risk of bias because of lack of blinding and imprecision due to small number of events of interest.

Benefits and harms

There was evidence from 11 randomised controlled trials regarding the comparison of dose regimens for the medical termination of pregnancy between 10^{+1} and 24^{+0} weeks of gestation. The randomised trials compared dose regimens with different misoprostol doses, misoprostol routes and mifepristone-misoprostol intervals. Despite the fact that there were more than 1 study reporting the comparison between 2 routes of administration or mifepristone-misoprostol intervals, pooling of results of the trials was not possible due to the difference in drug regimens, including the loading dose and intervals between two doses. Hence, pairwise comparison was conducted for all comparisons. The committee discussed that most studies included a loading dose of vaginal misoprostol in their regimen. The committee noted the biological plausibility of administering a loading dose in this gestation age group to harness the prostaglandin sensitivity. There was some evidence regarding the administration of misoprostol by oral, sublingual and vaginal routes following a loading dose of 800 mcg vaginal misoprostol. There was also evidence from dose regimens using buccal route of administration. The committee noted that presently, a loading dose of 800 mcg vaginal misoprostol is administered for the termination of pregnancy before 10 weeks, and discussed that using the same loading dose after 10 weeks would keep the loading dose regimen standardised and it would be operationally easier for the staff to follow the same regimen up to 24 weeks. Hence, the committee made the recommendation regarding the misoprostol loading dose regimen of 800 mcg vaginal misoprostol followed by 400 mcg doses of misoprostol every 3 hours until expulsion (vaginal, sublingual or buccal route). The committee recognised that, for some women vaginal route may not be the preferred route of administration. There was some evidence that there was no difference in time to expulsion, the rate of complete abortion and gastrointestinal side effects between sublingual and vaginal routes of misoprostol administration. Hence, the committee discussed that if vaginal route was not preferred by the woman, then a loading dose of misoprostol could be administered sublingually. The sublingual loading dose was taken from this study comparing regimens with loading dose of 800 mcg vaginal misoprostol and 600 mcg sublingual misoprostol.

Although only 1 trial directly compared the follow up dose of 400 mcg of misoprostol administered through oral, sublingual and vaginal routes but the vast majority of included studies used 400 mcg doses of misoprostol. Considering the weight of the evidence and the evidence from 1 trial showing that a direct comparison of 200 mcg with 400 mcg showed a longer time to expulsion with 200 mcg, the committee agreed that following the loading dose, 400 mcg of misoprostol should be offered every 3 hours until expulsion.

There was evidence that the time to expulsion was statistically significantly longer with the simultaneous administration of misoprostol with mifepristone or a shorter mifepristone-misoprostol interval. It was unclear whether there was a clinically important difference in the outcome between the treatment groups because the way it was reported in 3 studies (as medians) precluded the possibility of calculation of minimally important differences. The committee discussed that a shorter time to expulsion following larger interval between mifepristone and misoprostol administration was biologically plausible for the gestation age 10^{+1} to 24^{+0} weeks, as a larger fetus may benefit from a greater cervical dilation effect of mifepristone and sensitisation of the uterus. Time to expulsion was 1 of the critical outcomes for this review and hence, the committee agreed that misoprostol should be administered 36 to 48 hours after the administration of mifepristone for the termination of pregnancy between 10^{+1} and 24^{+0} weeks. The interval of 36 to 48 hours was chosen as there was evidence of effectiveness for dose regimens with this interval for vaginal and sublingual misoprostol with the same loading and follow-up doses, as included in the recommendation. It was also the most commonly used dosing interval in the included trials, reported in 4 out of 11 included trials.

The committee recognised that, sometimes it may not be possible to have the dosing interval of 36 to 48 hours between mifepristone and misoprostol as the women may not prefer a long

interval between the 2 drugs, either due to service provision or other factors making it less convenient for her. The committee agreed that convenience of women should be an important consideration, and hence, the committee agreed that, in such situations, a shorter mifepristone-misoprostol interval should be considered. However, the committee noted that, in such circumstances, the woman should be informed regarding the longer time to induction associated with a shorter duration between mifepristone and misoprostol administration.

As there was sufficient evidence to inform the recommendations, the committee decided to prioritise other areas addressed by the guideline for future research and therefore made no research recommendations regarding the optimal regimen and route of administration of misoprostol after mifepristone for inducing medical termination from 10^{+1} to 24^{+0} weeks.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The committee considered that there was unlikely to be a significant resource impact from the recommendations made. The use of oral misoprostol, which has a longer time to expulsion and higher number of adverse effects than vaginal or sublingual route, is likely to reduce with the recommendations. Any net effect of this change is likely to be cost saving with reduction in the hospitalisation time.

Other consideration

There was some evidence that vaginal and sublingual routes of administration were associated with a shorter time to expulsion and vaginal route was associated with fewer gastrointestinal side effects, when compared to oral route of administration of misoprostol. Hence, the committee did not make a recommendation about administering misoprostol by oral route. However, the committee discussed that practitioners could consider administering misoprostol orally for repeat doses if other routes of administration are not acceptable to the woman or not appropriate. The committee also noted that, when doing so, it is important that women are advised that oral administration of misoprostol is associated with a longer induction to expulsion interval than administration by other routes.

The committee were aware of guidelines from the Royal College of Obstetricians and Gynaecologists that recommend feticide is used for medical termination of pregnancy after 21^{+6} weeks' gestation, unless the termination is being conducted for lethal fetal anomaly or the woman does not wish feticide (RCOG 2010).

The evidence considered for this review question covered the gestational age range between 10^{+1} and 24^{+0} weeks' gestation. However, recommendations were made for women between 10^{+1} and 23^{+6} weeks' gestation to be consistent with the requirements of the 1967 Abortion Act.

References

Abbas 2016

Abbas, D. F., Blum, J., Ngoc, N. T. N., Nga, N. T. B., Chi, H. T. K., Martin, R., Winikoff, B.(2016). Simultaneous Administration Compared with a 24-Hour Mifepristone-Misoprostol Interval in Second-Trimester Abortion, Obstetrics and Gynecology, 128, 1077-1083.

Brouns 2010

Brouns, J. F. G. M., Van Wely, M., Burger, M. P. M., Van Wijngaarden, W. J. (2010). Comparison of two dose regimens of misoprostol for second-trimester pregnancy termination, Contraception, 82, 266-275.

Chai 2009

Chai, J., Tang, O. S., Hong, Q. Q., Chen, Q. F., Cheng, L. N., Ng, E., Ho, P. C..(2009). A randomized trial to compare two dosing intervals of misoprostol following mifepristone administration in second trimester medical abortion, Human Reproduction, 24, 320-324.

Dickinson 2014

Dickinson, J. E., Jennings, B. G., Doherty, D. A. (2014). Mifepristone and oral, vaginal, or sublingual misoprostol for second-trimester abortion: a randomized controlled trial, Obstetrics & GynecologyObstet Gynecol, 123, 1162-8.

El-Refaey 1995

El-Refaey, H., Templeton, A. (1995). Induction of abortion in the second trimester by a combination of misoprostol and mifepristone: A randomized comparison between two misoprostol regimens, 10, 475-478.

Hamoda 2005

Hamoda, H., Ashok, P. W., Flett, G. M. M., Templeton, A. (2005). A randomized trial of mifepristone in combination with misoprostol administered sublingually or vaginally for medical abortion at 13-20 weeks' gestation, Human Reproduction, 20, 2348-2354.

Ho 1997

Ho, P. C., Ngai, S. W., Liu, K. L., Wong, G. C. Y., Lee, S. W. H. (1997).Vaginal misoprostol compared with oral misoprostol in termination of second-trimester pregnancy, 90, 735-738.

Hou 2010

Hou,S., Zhang,L., Chen,Q., Fang,A., Cheng,L.(2010). One- and two-day mifepristone-misoprostol intervals for second trimester termination of pregnancy between 13 and 16 weeks of gestation, International Journal of Gynaecology and Obstetrics, 111, 126-130.

Mentula 2011

Mentula, M, Suhonen, S, Heikinheimo, O. (2011). One- and two-day dosing intervals between mifepristone and misoprostol in second trimester medical termination of pregnancy--a randomized trial, Human reproduction (Oxford, England), 26, 2690-2697.

Ngai 2000

Ngai, S. W., Tang, O. S., Ho, P. C. (2000). Randomized comparison of vaginal (200 mug every 3 h) and oral (400 mug every 3 h) misoprostol when combined with mifepristone in termination of second trimester pregnancy, Human Reproduction, 15, 2205-2208.

RCOG 2010

Royal College of Obstetricians and Gynaecologists (2010). Termination of pregnancy for fetal abnormality in England, Scotland and Wales: Report of a Working Party.

Tang 2005

Tang, O. S., Chan, C. C. W., Kan, A. S. Y., Ho, P. C. (2005). A prospective randomized comparison of sublingual and oral misoprostol when combined with mifepristone for medical abortion at 12-20 weeks' gestation, Human Reproduction, 20, 3062-3066.

Appendices

Appendix A – Review protocols

Review protocol for review question: What is the optimal regimen and route of administration of misoprostol after mifepristone, for inducing medical termination from 10^{+1} to 24^{+0} weeks?

Field (based on PRISMA-P	Content
Review question in SCOPE	What is the optimal dose and route of administration of misoprostol after mifepristone, for inducing medical termination in the second trimester?
Review question in guideline	What is the optimal regimen and route of administration of misoprostol after mifepristone, for inducing medical termination from 10+1 to 24+0 weeks
Type of review question	Intervention
Objective of the review	To determine the optimal regimen and route of administration for misoprostol (after mifepristone) between 10+1 and 24+0 weeks' gestation
Eligibility criteria – population	Women who are having a medical termination of pregnancy between 10+1 and 24+0 weeks' gestation Exclusions: - Any studies with an indirect population
Eligibility criteria – intervention(s)	Route of misoprostol administration: • Vaginal • Oral • Sublingual • Buccal Dose of misoprostol: • 200 mcg • 400 mcg • 600 mcg • 800 mcg Dose interval
Eligibility criteria – comparator(s)/control	All combinations of the routes of administration, doses, number of doses, and dosing intervals listed above will be compared.
Outcomes and prioritisation	**Critical outcomes:** • Time to expulsion • Complete abortion without the need for surgical intervention • Incomplete abortion with the need for surgical intervention

Field (based on PRISMA-P	Content
	Important outcomes: • Haemorrhage requiring transfusion or > 500 ml of blood loss • Vomiting • Patient satisfaction • Diarrhoea
Eligibility criteria – study design	- Systematic reviews of RCTs - RCTs
Other inclusion exclusion criteria	Inclusion: - English-language
Proposed sensitivity/sub-group analysis, or meta-regression	Stratified analyses based on the following sub-groups of women, where possible: Medical conditions: - Complex pre-existing medical conditions - No complex pre-existing medical conditions Gestational age: - 10+1 weeks to 13+6 weeks - 14+0 weeks to 24+0 weeks Caesarean section: - Previous caesarean section - No previous caesarean section Parity: - Nulliparous - Parous
Selection process – duplicate screening/selection/analysis	Dual weeding will not be performed for this question Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual data extraction will not be performed for this question.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations,
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design):

Field (based on PRISMA-P	Content
	Apply standard animal/non-English language exclusion Limit to RCTs and systematic reviews Dates: from 1985 Only studies conducted from 1985 onwards will be considered for this review question, as mifepristone was made available in the UK in 1991 and evidence to support the use of mifepristone in practice is unlikely to be more than 5 years before its licensing in 1991.
Identify if an update	Not an update
Author contacts	For details please see the guideline in development web site.
Highlight if amendment to previous protocol	For details please see Section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix B
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or appendix H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or appendix H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists will be used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • RoBIS for systematic reviews • Cochrane risk of bias tool for RCTs The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see Section 6.4 of Developing NICE guidelines: the manual
Methods for analysis – combining studies and exploring (in)consistency	Synthesis of data: Pairwise meta-analysis will be conducted where appropriate for all other outcomes. When meta-analysing continuous data, change scores will be pooled in preference to final scores. For details regarding inconsistency, please see the methods chapter

Field (based on PRISMA-P	Content
	Minimally important differences: 'Haemorrhage requiring transfusion or >500 loss': Statistical significance 'Complete abortion without the need for surgical intervention': 3% (with the upper limit of the 95% CI ≤ 5%) All other outcomes default values will be used of: 0.8 and 1.25 for dichotomous outcomes (relative risks); 0.5 times SD (of the control group) for continuous outcomes
Meta-bias assessment – publication bias, selective reporting bias	For details please see Section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots.
Assessment of confidence in cumulative evidence	For details please see Sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by The National Guideline Alliance and chaired by Profession Iain Cameron in line with section 3 of Developing NICE guidelines: the manual. Staff from The National Guideline Alliance will undertake systematic literature searches, appraise the evidence, conduct meta-analysis and cost-effectiveness analysis where appropriate, and draft the guideline in collaboration with the committee. For details please see the methods chapter.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds The National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England
PROSPERO registration number	Not registered

CI: confidence interval; GRADE: Grading of Recommendations Assessment, Development and Evaluation; mcg: micrograms; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NGA: National Guideline Alliance; RCT: randomised controlled trial; RoBIS: risk of bias in systematic reviews; SD: standard deviation

Appendix B – Literature search strategies

Literature search strategy for review question: What is the optimal regimen and route of administration of misoprostol after mifepristone, for inducing medical termination from 10^{+1} to 24^{+0} weeks?

The search for this topic was last run on 14th June 2018. It was decided not to undertake a re-run for this topic in November 2018 as this is not a fast moving evidence base and there were unlikely to be any new studies published which would affect the recommendations.

Database: Medline & Embase (Multifile)
Last searched on **Embase Classic+Embase** 1947 to 2018 June 13, **Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R**) 1946 to Present
Date of last search: 14th June 2018

#	Searches
1	exp abortion/ use emczd
2	exp pregnancy termination/ use emczd
3	exp Abortion, Induced/ use ppez
4	Abortion Applicants/ use ppez
5	exp Abortion, Spontaneous/ use ppez
6	exp Abortion, Criminal/ use ppez
7	Aborted fetus/ use ppez
8	fetus death/ use emczd
9	abortion.mp.
10	(abort$ or postabort$ or preabort$).mp.
11	((f?etal$ or f?etus$ or gestat$ or midtrimester$ or pregnan$ or prenatal$ or pre natal$ or trimester$) and terminat$).mp.
12	((f?etal$ or f?etus$) adj loss$).mp.
13	((gestat$ or midtrimester$ or pregnan$ or prenatal$ or pre natal$ or trimester$) adj3 loss$).mp.
14	(((elective$ or threaten$ or voluntar$) adj3 interrupt$) and pregnan$).mp.
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16	Misoprostol/ use ppez
17	misoprostol/ use emczd
18	(misoprostol$ or cytotec$ or arthrotec$ or oxaprost$ or cyprostol$ or mibetec$ or prostokos$ or misotrol$).mp.
19	16 or 17 or 18
20	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
21	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
22	meta-analysis/
23	meta-analysis as topic/
24	systematic review/
25	meta-analysis/
26	(meta analy* or metanaly* or metaanaly*).ti,ab.
27	((systematic or evidence) adj2 (review* or overview*)).ti,ab.

#	Searches
28	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
29	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
30	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
31	(search* adj4 literature).ab.
32	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
33	cochrane.jw.
34	((pool* or combined) adj2 (data or trials or studies or results)).ab.
35	letter/
36	editorial/
37	news/
38	exp historical article/
39	Anecdotes as Topic/
40	comment/
41	case report/
42	(letter or comment*).ti.
43	35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
44	randomized controlled trial/ or random*.ti,ab.
45	43 not 44
46	animals/ not humans/
47	exp Animals, Laboratory/
48	exp Animal Experimentation/
49	exp Models, Animal/
50	exp Rodentia/
51	(rat or rats or mouse or mice).ti.
52	45 or 46 or 47 or 48 or 49 or 50 or 51
53	letter.pt. or letter/
54	note.pt.
55	editorial.pt.
56	case report/ or case study/
57	(letter or comment*).ti.
58	53 or 54 or 55 or 56 or 57
59	randomized controlled trial/ or random*.ti,ab.
60	58 not 59
61	animal/ not human/
62	nonhuman/
63	exp Animal Experiment/
64	exp Experimental Animal/
65	animal model/
66	exp Rodent/
67	(rat or rats or mouse or mice).ti.
68	60 or 61 or 62 or 63 or 64 or 65 or 66 or 67
69	52 use ppez
70	68 use emczd
71	69 or 70

#	Searches
72	20 use ppez
73	21 use emczd
74	72 or 73
75	(or/22-23,26,28-33) use ppez
76	(or/24-27,29-34) use emczd
77	75 or 76
78	15 and 19
79	71 and 78
80	78 not 79
81	74 or 77
82	80 and 81
83	remove duplicates from 82
84	limit 83 to english language
85	limit 84 to yr="1985 -Current"

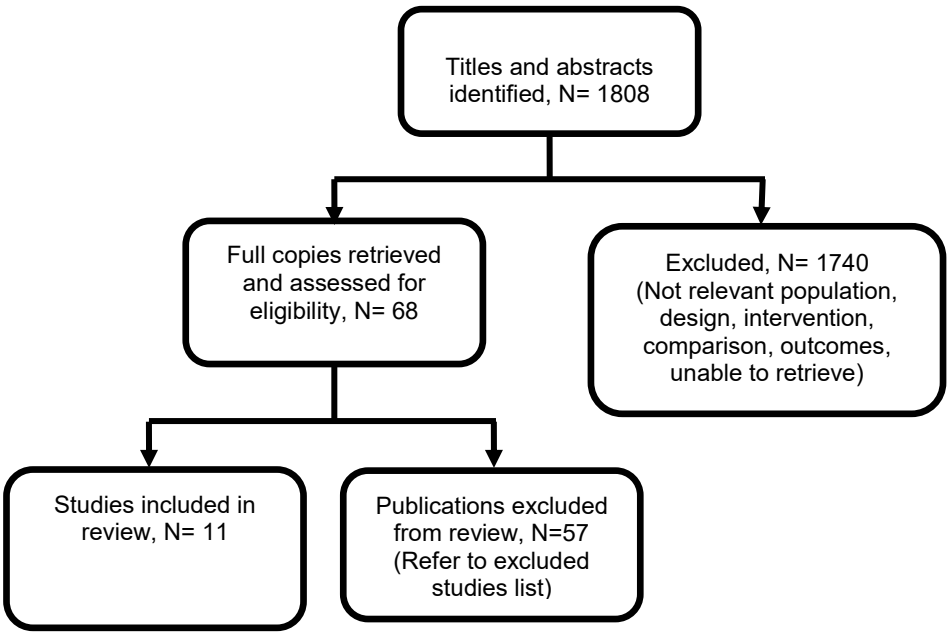
Database: Cochrane Library via Wiley Online
Date of last search: 14th June 2018

#	Searches
#1	MeSH descriptor: [Abortion, Induced] explode all trees
#2	MeSH descriptor: [Abortion Applicants] explode all trees
#3	MeSH descriptor: [Abortion, Spontaneous] explode all trees
#4	MeSH descriptor: [Abortion, Criminal] explode all trees
#5	MeSH descriptor: [Aborted Fetus] explode all trees
#6	"abortion":ti,ab,kw (Word variations have been searched)
#7	(abort* or postabort* or preabort*):ti,ab,kw (Word variations have been searched)
#8	((fetal* or fetus* or foetal* or foetus* or gestat* or midtrimester* or pregnan* or prenatal* or pre natal* or trimester*) and terminat*):ti,ab,kw (Word variations have been searched)
#9	((fetal* or fetus* or foetal* or foetus*) next loss*):ti,ab,kw (Word variations have been searched)
#10	((gestat* or midtrimester* or pregnan* or prenatal* or pre natal* or trimester*) near/3 loss*):ti,ab,kw (Word variations have been searched)
#11	(((elective* or threaten* or voluntar*) near/3 interrupt*) and pregnan*):ti,ab,kw (Word variations have been searched)
#12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
#13	MeSH descriptor: [Misoprostol] this term only
#14	(misoprostol* or cytotec* or arthrotec* or oxaprost* or cyprostol* or mibetec* or prostokos* or misotrol*):ti,ab,kw (Word variations have been searched)
#15	#13 or #14
#16	#12 and #15

Appendix C – Clinical evidence study selection

Clinical evidence study selection for review question: What is the optimal regimen and route of administration of misoprostol after mifepristone, for inducing medical termination from 10^{+1} to 24^{+0} weeks?

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What is the optimal regimen and route of administration of misoprostol after mifepristone, for inducing medical termination from 10^{+1} to 24^{+0} weeks?

Study details	Participants	Interventions	Outcomes and Results	Comments
Full citation Abbas, D. F., Blum, J., Ngoc, N. T. N., Nga, N. T. B., Chi, H. T. K., Martin, R., Winikoff, B., Simultaneous Administration Compared with a 24-Hour Mifepristone-Misoprostol Interval in Second-Trimester Abortion, Obstetrics and Gynecology, 128, 1077-1083, 2016 **Ref Id** 773208 **Country/ies where the study was carried out** Vietnam **Study type** Double blind randomized controlled trial	**Sample size** n=505 **Characteristics** Age, mean (standard deviation): Simultaneous administration of mifepristone and misoprostol (n=254): 24 (6) years; 24 hour interval between mifepristone and misoprostol (n=251): 24 (6) years Gestational age, mean (standard deviation): Simultaneous administration of mifepristone and misoprostol (n=254): 16.4 (2.8) weeks; 24 hour interval between mifepristone	**Simultaneous administration of mifepristone and misoprostol:** Placebo followed 24 hours later by 200 mg mifepristone and 400 mcg buccal misoprostol followed by 400 mcg buccal misoprostol every 3 hours until expulsion of foetus or 48 hours **24 hour interval between mifepristone and misoprostol:** 200 mg mifepristone followed 24 hours later by 200 mg placebo and 400 mcg buccal misoprostol followed by 400 mcg buccal misoprostol every 3 hours until expulsion of foetus or 48 hours	**Outcome: Time to expulsion, median (range)** Simultaneous administration of mifepristone and misoprostol (n=254): 13.0 (4.9 to 47.8) hours; 24 hour interval between mifepristone and misoprostol (n=251): 7.7 (2.1 to 40.3) hours **Outcome: Complete abortion without the need for surgical intervention (at 48 hours)** Simultaneous administration of mifepristone and misoprostol: 243/254; 24 hour interval between mifepristone and misoprostol: 243/251 **Outcome: Incomplete abortion with the need for surgical intervention**	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: unclear risk, not reported Allocation concealment: low risk , sealed envelopes used for allocation Blinding of participants and personnel: low risk; double blinding Blinding of outcome assessment: low risk; blinding till the end of data collection Attrition bias: low risk; 4 exclusions; lost to follow up:2; protocol violations: 2;reasons of exclusion are described and number of women lost to follow-up is same in both groups(1 each) Selective reporting: low risk; all outcomes reported in sufficient detail for analysis

Study details	Participants	Interventions	Outcomes and Results	Comments
Aim of the study To compare the efficacy of two dose regimens; with misoprostol, administered either simultaneously, or after 24 hour interval following 200 mg mifepristone for second trimester abortion. **Study dates** February 19, 2013 to April 29, 2014 **Source of funding** Supported by an anonymous donor with the declaration that the funder had no role in the development of the study question or the study design or in the collection, storage, or analysis of data	and misoprostol (n=251): 16.4 (2.9) weeks **Inclusion criteria** 1) Women with a live foetus 2) Gestational age 13 to 22 weeks 3) Eligible for medical termination of pregnancy as determined by clinical history and examination 4) Closed cervical os 5) No vaginal bleeding 6) No known contraindications to the study drugs **Exclusion criteria** 1) History of trans mural uterine incision 2) Contraindications to vaginal delivery 3) Parity more than 5 4) Those in active labour 5) Signs of infection	Those who failed to abort with these regimens were given a repeat dose of misoprostol up to 5 doses. Those failing to abort with repeat dose were treated with gemeprost.	Simultaneous administration of mifepristone and misoprostol: 2/254; 24 hour interval between mifepristone and misoprostol: 1/251 **Outcome: Haemorrhage requiring transfusion or >500ml of blood loss** Simultaneous administration of mifepristone and misoprostol: 1/254; 24 hour interval between mifepristone and misoprostol: 0/251 **Outcome: Vomiting** Simultaneous administration of mifepristone and misoprostol: 63/254; 24 hour interval between mifepristone and misoprostol: 57/251 **Outcome: Patient satisfaction (procedure satisfactory or very satisfactory)**	**Other information** None

Study details	Participants	Interventions	Outcomes and Results	Comments
			Simultaneous administration of mifepristone and misoprostol: 252/254; 24 hour interval between mifepristone and misoprostol: 249/251 **Outcome: Diarrhoea** Simultaneous administration of mifepristone and misoprostol: 137/254; 24 hour interval between mifepristone and misoprostol: 83/251	
Full citation Brouns, J. F. G. M., Van Wely, M., Burger, M. P. M., Van Wijngaarden, W. J., Comparison of two dose regimens of misoprostol for second-trimester pregnancy termination, Contraception, 82, 266-275, 2010 **Ref Id** 801899 **Country/ies where the study was carried out**	**Sample size** n=176 **Characteristics** Age, mean (standard deviation) 200 mcg vaginal misoprostol (n=86): 31.1 (6.3) years; 400 mcg vaginal misoprostol (n=90): 32.6 (6.1) years Duration of amenorrhea, mean(standard deviation)	**200 mcg vaginal misoprostol:** 200 mcg vaginal misoprostol at 4 hour intervals, 36 to 48 hours following oral mifepristone 200 mg **400 mcg vaginal misoprostol:** 400 mcg vaginal misoprostol at 4 hour intervals, 36 to 48 hours following oral mifepristone 200 mg Misoprostol was repeated every 4 hours until expulsion, up to 5 doses per	**Outcome: Time to expulsion, median (range)** 200 mcg vaginal misoprostol (n=86): 9.2 (7.1 to 11.3) hours; 400 mcg vaginal misoprostol (n=90): 8.0 (7.1 to 8.9) hours **Outcome: Complete abortion without the need for surgical intervention (at 48 hours)** 200 mcg vaginal misoprostol: 57/86;	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: low risk, computer-generated randomization Allocation concealment: low risk, non-transparent non-labelled carbon paper applicators placed in brown, non-transparent paper bags with only the trial number on it Blinding of participants and personnel: low risk; double blinding Blinding of outcome assessment: low risk; blinding till the end of data collection

Study details	Participants	Interventions	Outcomes and Results	Comments
The Netherlands **Study type** Double blind randomized controlled trial **Aim of the study** To compare the efficacy of 2 dose regimens of misoprostol administered vaginally with 200 mg mifepristone for second trimester termination of viable and non-viable pregnancies. **Study dates** October 2000 to September 2004 **Source of funding** The Mimis trial was funded by the Department of Obstetrics and Gynecology of the Academic Medical Center (AMC) Amsterdam.	200 mcg vaginal misoprostol (n=86): 134 (22.7) weeks; 400 mcg vaginal misoprostol (n=90): 136 (21.8) weeks **Inclusion criteria** 1) Gestational age between 14 and 24 weeks confirmed by ultrasound 2) Request for termination of pregnancy **Exclusion criteria** 1) No informed consent 2) History of allergic reaction to mifepristone or misoprostol 3) Chronic adrenal gland insufficiency 4) Kidney or liver problems 5) Continuous use of corticosteroid medication	24 hours, and a maximum of 10 doses in 48 hours.	400 mcg vaginal misoprostol : 66/90 **Outcome: Incomplete abortion with the need for surgical intervention** 200 mcg vaginal misoprostol: 29/86; 400 mcg vaginal misoprostol : 24/90 **Outcome: Haemorrhage requiring transfusion or >500ml of blood loss** 200 mcg vaginal misoprostol: 4/86; 400 mcg vaginal misoprostol: 3/90 **Outcome: Vomiting** 200 mcg vaginal misoprostol 27/86; 400 mcg vaginal misoprostol: 37/90 **Outcome: Diarrhoea** 200 mcg vaginal misoprostol: 5/86; 400 mcg vaginal misoprostol: 10/90	Attrition bias: low risk for all outcomes;176/176 randomized were analysed Selective reporting: low risk; all outcomes reported in sufficient detail for analysis **Other information** None

Study details	Participants	Interventions	Outcomes and Results	Comments
	6) Severe pulmonary disease, cardiovascular disease or glaucoma			
Full citation Chai, J., Tang, O. S., Hong, Q. Q., Chen, Q. F., Cheng, L. N., Ng, E., Ho, P. C., A randomized trial to compare two dosing intervals of misoprostol following mifepristone administration in second trimester medical abortion, Human Reproduction, 24, 320-324, 2009 **Ref Id** 815828 **Country/ies where the study was carried out** China **Study type** Randomized controlled trial **Aim of the study**	**Sample size** n=141 **Characteristics** Age, mean (standard deviation) Simultaneous administration of mifepristone and misoprostol (n=71): 25.5 (5.4) years; 36 to 38 hour interval between mifepristone and misoprostol (n=70): 25.1(5.5) years **Inclusion criteria** 1) Healthy women aged more than 18 years 2) Those requesting termination of pregnancy 3) Second trimester pregnancy at 12 to 20 weeks of gestation	**Simultaneous administration of mifepristone and misoprostol:** 200 mg mifepristone orally followed by 600 mcg vaginal misoprostol immediately, which was then followed by 400 mcg vaginal misoprostol every 3 hours up to 4 doses **36 to 38 hour interval between mifepristone and misoprostol:** 200 mg mifepristone orally followed by 600 mcg vaginal misoprostol 36 to 38 hours later followed by 400 mcg vaginal misoprostol every 3 hours up to 4 doses Follow-up assessment was done 8 weeks after the termination of pregnancy, or earlier if medically indicated	**Outcome: Time to expulsion, median(range)** Simultaneous administration of mifepristone and misoprostol (n=71): 10.0 (3.5 to 126) hours; 36 to 38 hour interval between mifepristone and misoprostol (n=70): 4.9 (1.8 to 13.8) hours **Outcome: Complete abortion without the need for surgical intervention(at 48 hours)** Simultaneous administration of mifepristone and misoprostol: 70/71; 36 to 38 hour interval between mifepristone and misoprostol : 70/70 **Outcome: Incomplete abortion with the need for surgical intervention** Simultaneous administration of mifepristone and misoprostol: 5/71;	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: low risk; computer-generated randomization Allocation concealment: low risk; sealed, opaque envelopes used for allocation Blinding of participants and personnel: blinding not feasible; low risk for objective outcomes, high risk for subjective outcomes Blinding of outcome assessment: blinding not feasible; low risk for objective outcomes, high risk for subjective outcomes Attrition bias: low risk for all outcomes;141/141 randomized were analysed Selective reporting: low risk, all outcomes reported in sufficient detail for analysis **Other information** None

Study details	Participants	Interventions	Outcomes and Results	Comments
To compare simultaneous administration to 36 to 38 hour interval of misoprostol dose after pre-treatment with mifepristone for second trimester medical abortion. **Study dates** June 2006 to September 2007 **Source of funding** Funded by the Committee on Research and Conference Grants of University of Hong Kong	4) Those willing to comply with follow-up visits schedule **Exclusion criteria** 1) Contraindications to mifepristone, like adrenal disease or steroid-dependent cancer 2) Contraindications to misoprostol like mitral stenosis glaucoma, sickle cell anaemia, diastolic pressure over 100 mm Hg, severe asthma or known allergy to prostaglandin 3) History or evidence of thrombo-embolism, severe or recurrent liver disease or pruritus of pregnancy 4) Known history of or active medical disease 5) History of regular use of prescription drugs		36 to 38 hour interval between mifepristone and misoprostol : 1/70 **Outcome: Haemorrhage requiring transfusion or >500 ml of blood loss** Simultaneous administration of mifepristone and misoprostol:0/71; 36 to 38 hour interval between mifepristone and misoprostol : 0/70 **Outcome: Diarrhoea** Simultaneous administration of mifepristone and misoprostol:18/71; 36 to 38 hour interval between mifepristone and misoprostol: 10/70	

Study details	Participants	Interventions	Outcomes and Results	Comments
	6) Intrauterine contraceptive device 7) Haemoglobin level 100 g/l or abnormal liver or renal function tests 8) Breastfeeding 9) Heavy smoker, those consuming more than 20 cigarettes per day			
Full citation Dickinson, J. E., Jennings, B. G., Doherty, D. A., Mifepristone and oral, vaginal, or sublingual misoprostol for second-trimester abortion: a randomized controlled trial, Obstetrics & Gynecology Obstet Gynecol, 123, 1162-8, 2014 **Ref Id** 771421 **Country/ies where the study was carried out** Australia	**Sample size** N=302 **Characteristics** Age, median (interquartile range) Oral misoprostol (n=100):32 (28 to 36) years; Vaginal misoprostol (n=100): 31 (28 to 35) years; Sublingual misoprostol (n=102): 32 (28 to 37) years Gestational age, median (interquartile range)	**Oral misoprostol:** mifepristone 200 mg followed 24 to 48 hours later by 800 mcg vaginal misoprostol followed by 400 mcg oral misoprostol every 3 hours up to 5 doses **Vaginal misoprostol:** mifepristone 200 mg followed 24 to 48 hours later by 800 mcg vaginal misoprostol followed by 400 mcg vaginal misoprostol every 4 hours up to 5 doses **Sublingual misoprostol:** mifepristone 200 mg followed 24 to 48 hours later by 800 mcg vaginal	**Outcome: Time to expulsion, median (range)** Oral misoprostol (n=100): 9.5 (8.5 to 11.4) hours; Vaginal misoprostol (n=100): 7.4 (6.5 to 8.2) hours; Sublingual misoprostol (n=102): 7.8 (7.0 to 9.2) hours **Outcome: Haemorrhage requiring transfusion or >500 ml of blood loss** Oral misoprostol: 2/100; Vaginal misoprostol: 1/100; Sublingual misoprostol: 2/102 **Outcome: Patient satisfaction, median (interquartile range)**	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: low risk, computer-generated random sequence in blocks of 30 with 10 protocols per group Allocation concealment: low risk; series of sealed opaque envelopes for allocation Blinding of participants and personnel: no blinding; not practical to blind the women and staff ,low risk for objective outcomes, high risk for subjective outcomes Blinding of outcome assessment: no blinding; not feasible to blind low risk for

Study details	Participants	Interventions	Outcomes and Results	Comments
Study type Randomized controlled trial **Aim of the study** To compare the efficacy of the vaginal, sublingual and oral misoprostol after mifepristone priming in second-trimester medical abortion. **Study dates** April 2009 to April 2013 **Source of funding** Not reported	Oral misoprostol (n=100) : 19.1 (17.2 to 20.8) weeks; Vaginal misoprostol (n=100): 19.4 (17.3 to 20.4) weeks; Sublingual misoprostol (n=102): 19.7 (17.6 to 21.0) weeks **Inclusion criteria** Women admitted to King Edward Memorial Hospital for Women, Perth, for second trimester medical termination of pregnancy for foetal abnormality or maternal medical complication at 14 to 24 weeks of gestation **Exclusion criteria** Not reported	misoprostol followed by 400 mcg sublingual misoprostol every 3 hours up to 5 doses If expulsion did not occur after the completion of the misoprostol regimen, the regimen was repeated 12 hours after the last misoprostol dose was completed. The mifepristone dose was not repeated.	0 to 100 visual analogue scale (0-best; 100-worst) Oral misoprostol (n=100): Opinion of procedure: 50 (20 to 50) Vaginal misoprostol (n=100): Opinion of procedure: 50(26 to 50) Sublingual misoprostol (n=102):Opinion of procedure: 50 (19 to 50)	objective outcomes, high risk for subjective outcomes Attrition bias: low risk for all outcomes; 302/302 randomized were analysed Selective reporting: high risk, outcomes like diarrhoea, vomiting not reported in sufficient detail for analysis **Other information** None
Full citation El-Refaey, H., Templeton, A., Induction of abortion in the second trimester by a combination of	**Sample size** n=69 **Characteristics**	**Vaginal misoprostol:** 600 mg mifepristone orally followed by 600 mcg vaginal misoprostol 36 to 48 hours later and then misoprostol	**Outcome: Time to expulsion, mean(range)** Vaginal misoprostol (n=35): 6.0 (5.0 to 7.2) hours;	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool

Study details	Participants	Interventions	Outcomes and Results	Comments
misoprostol and mifepristone: A randomized comparison between two misoprostol regimens, 10, 475-478, 1995 **Ref Id** 839103 **Country/ies where the study was carried out** United Kingdom **Study type** Randomized controlled trial **Aim of the study** To compare the efficacy of 2 dose regimens of misoprostol with first dose administered vaginally with oral mifepristone, followed by a comparison of subsequent vaginal and oral administration of misoprostol for second trimester termination of	Age, mean (standard deviation): Vaginal misoprostol (n=35) : 21.7 (6.5) years; Oral misoprostol (n=34) : 21.2 (6.5) years Gestational age, mean (standard deviation): Vaginal misoprostol (n=35): 108.2(12) days; Oral misoprostol (n=34): 110.0(12) days **Inclusion criteria** Pregnancies between 13 and 20 weeks, as confirmed by ultrasound scan examination, terminating for socioeconomic reasons **Exclusion criteria** Not reported	400 mcg vaginal every 3 hours up to 4 doses. **Oral misoprostol:** 600 mg mifepristone orally followed by 600 mcg vaginal misoprostol 36 to 48 hours later and then 400 mcg oral misoprostol every 3 hours up to 4 doses. If termination of pregnancy did not occur after 5 doses of misoprostol, the treatment was considered a failure and gemeprost 1 mg was administered vaginally.	Oral misoprostol (n=34): 6.7 (5.8 to 7.6) hours **Outcome: Complete abortion without the need for surgical intervention (at 48 hours)** Vaginal misoprostol: 34/35; Oral misoprostol: 33/34 **Outcome: Haemorrhage requiring transfusion or >500 ml of blood loss** Vaginal misoprostol: 0/35; Oral misoprostol: 0/34 **Outcome: Vomiting** Vaginal misoprostol: 20/35; Oral misoprostol: 21/34 **Outcome: Diarrhoea** Vaginal misoprostol: 10/35; Oral misoprostol: 12/34	Random sequence generation: low risk; computer-generated random number tables Allocation concealment: low risk; series of sealed opaque envelopes for allocation Blinding of participants and personnel: no blinding; blinding not practical, low risk for objective outcomes, high risk for subjective outcomes Blinding of outcome assessment: no blinding; blinding not practical, low risk for objective outcomes, high risk for subjective outcomes Attrition bias: low risk for all outcomes; 69/70 randomized were analysed Selective reporting: low risk; all outcomes reported in sufficient detail for analysis **Other information** None

Study details	Participants	Interventions	Outcomes and Results	Comments
viable and non-viable pregnancies. **Study dates** Not reported **Source of funding** Not reported				
Full citation Hamoda, H., Ashok, P. W., Flett, G. M. M., Templeton, A., A randomized trial of mifepristone in combination with misoprostol administered sublingually or vaginally for medical abortion at 13-20 weeks gestation, Human Reproduction, 20, 2348-2354, 2005 **Ref Id** 773040 **Country/ies where the study was carried out** United Kingdom **Study type**	**Sample size** n=76 **Characteristics** Age, mean (standard deviation) Sublingual misoprostol(n=36): 25 (6.72) years; Vaginal misoprostol(n=40): 23 (5.14) years **Inclusion criteria** 1) Viable singleton intrauterine pregnancy (confirmed by ultrasound scan) 2) Women requesting medical abortion between 13 and 20 weeks' gestation	**Sublingual misoprostol:** 200 mg mifepristone followed 36 to 48 hours later by 600 mcg sublingual misoprostol. Further 3 hourly doses of 400 mcg sublingual misoprostol up to 5 doses **Vaginal misoprostol:** 200 mg mifepristone followed 36 to 48 hours later by vaginal misoprostol 800 mcg. Further 3 hourly doses of 400 mcg vaginal misoprostol up to 5 doses If termination of pregnancy did not occur within 3 hours of the 5th dose of misoprostol, mifepristone 200 mg orally and further vaginal administration of misoprostol was offered.	**Outcome: Time to expulsion, median (range)** Sublingual misoprostol (n=36): 5.27 (0.55 to 29.35) hours; Vaginal misoprostol (n=40): 5.40(2.10 to 13.00) hours **Outcome: Incomplete abortion with the need for surgical intervention** Sublingual misoprostol: 3/36; Vaginal misoprostol: 1/40 **Outcome: Vomiting** Sublingual misoprostol: 25/36; Vaginal misoprostol: 25/40 **Outcome: Patient satisfaction (Satisfied)** Sublingual misoprostol: 24/36;	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: low risk; randomization with random number tables Allocation concealment: low risk; consecutive sealed envelopes used for allocation Blinding of participants and personnel: no blinding; low risk for objective outcomes, high risk for subjective outcomes Blinding of outcome assessment: no blinding; low risk for objective outcomes, high risk for subjective outcomes Attrition bias: low risk for all outcomes; 69/76 randomized were analysed, with similar withdrawal rates in both groups,

Study details	Participants	Interventions	Outcomes and Results	Comments
Randomized controlled trial **Aim of the study** To assess the efficacy and acceptability of sublingual compared to vaginal misoprostol following mifepristone for medical abortion in the second trimester **Study dates** April 2003 to September 2004 **Source of funding** Not reported	**Exclusion criteria** 1) Age under 16 years 2) Severe asthma 3) Haemorrhagic disorders and treatment with anticoagulants 4) Known allergy to prostaglandins 5) History of cardiac disease 6) Smoking 7) Over the age of 35 years with ECG abnormalities 8) Breast feeding		Vaginal misoprostol: 25/40 **Outcome: Diarrhoea** Sublingual misoprostol:19/36; Vaginal misoprostol: 21/40	with reasons of exclusion clearly described Selective reporting: low risk; all outcomes reported in sufficient detail for analysis **Other information** None
Full citation Ho, P. C., Ngai, S. W., Liu, K. L., Wong, G. C. Y., Lee, S. W. H., Vaginal misoprostol compared with oral misoprostol in termination of second-trimester pregnancy, 90, 735-738, 1997 **Ref Id**	**Sample size** n=98 **Characteristics** Age, mean (standard deviation) Oral misoprostol (n=49): 20.5 (4.0) years;	**Oral misoprostol:** 200 mg mifepristone followed 36 to 48 hours later by 200 mcg oral misoprostol and vaginal placebo every 3 hours up to 5 doses **Vaginal misoprostol :** 200 mg mifepristone followed 36 to 48 hours later by 200 mcg misoprostol	**Outcome: Time to expulsion, mean (standard deviation)** Oral misoprostol: 27.8 (31.7) hours; Vaginal misoprostol: 14.8 (18.2) hours **Outcome: Complete abortion without the need**	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: low risk; list of random numbers used for randomization Allocation concealment: low risk; process not described but mentioned that the

Study details	Participants	Interventions	Outcomes and Results	Comments
839108 **Country/ies where the study was carried out** China **Study type** Randomized controlled trial **Aim of the study** To compare the effectiveness of vaginal and oral misoprostol for second trimester termination of pregnancy following pre-treatment with mifepristone **Study dates** Not reported **Source of funding** Supported by Task force of postovulatory methods of fertility regulation, special programme of research, Development and Research Training in Human Reproduction, the	Vaginal misoprostol (n=49): 20.9 (4.8) years **Inclusion criteria** 1) Good general health 2) Age 16 to 35 years 3) Singleton pregnancy 4) Gestational age 14 to 20 weeks **Exclusion criteria** 1) Past or present ill health 2) Nursing mothers 3) Intrauterine contraceptive device 4) Smoking >10 cigarettes /day	vaginally and a placebo orally every 3 hours up to 5 doses Those who failed to abort with the above regimen, were given a repeat dose of misoprostol up to 5 doses. Those failing to abort with repeat dose were treated with gemeprost.	**for surgical intervention (48 hours)** Oral misoprostol: 29/49; Vaginal misoprostol : 36/49 **Outcome: Incomplete abortion with the need for surgical intervention** Oral misoprostol: 0/49; Vaginal misoprostol: 0/49 **Outcome: Vomiting** Oral misoprostol: 10/49; Vaginal misoprostol: 14/49 **Outcome: Diarrhoea** Oral misoprostol: 16/49; Vaginal misoprostol: 9/49	schedule allocation was unknown to the clinicians Blinding of participants and personnel: low risk, use of placebo and schedule unknown to participants Blinding of outcome assessment: unclear risk, not described Attrition bias: low risk for all outcomes;98/98 randomized were analysed Selective reporting: low risk; all outcomes reported in sufficient detail for analysis **Other information** None

Study details	Participants	Interventions	Outcomes and Results	Comments
World Health Organization				
Full citation Hou,S., Zhang,L., Chen,Q., Fang,A., Cheng,L., One- and two-day mifepristone-misoprostol intervals for second trimester termination of pregnancy between 13 and 16 weeks of gestation, International Journal of Gynaecology and Obstetrics, 111, 126-130, 2010 **Ref Id** 154617 **Country/ies where the study was carried out** China **Study type** Randomized Controlled trial **Aim of the study** To compare the effectiveness of 1 day	**Sample size** n=100 **Characteristics** Age, mean(standard deviation) 1 day interval: n=50): 26.2(6.4) years; 2 day interval: n=50): 24.6(6.3) years Gestational age, mean (standard deviation) 1 day interval (n=50): 13.8 (0.7) weeks; 2 day interval (n=50): 13.9 (0.9) weeks **Inclusion criteria** 1) Healthy women between 18 and 45 years age 2) Request for termination of an unwanted pregnancy	**1 day interval:** 200 mg oral mifepristone followed 1 day later by 600 mcg vaginal misoprostol and 400 mcg oral misoprostol every 6 hours up to 2 doses **2 day interval:** 200 mg oral mifepristone followed 2 days later by 600 mcg vaginal misoprostol and 400 mcg oral misoprostol every 6 hours up to 2 doses The women were asked to return for a follow-up assessment 8 weeks after termination.	**Outcome: Time to expulsion, mean(standard deviation)** 1 day interval (n=50): 7.0 (3.0) hours; 2 day interval (n=50): 6.8 (4.3) hours **Outcome: Complete abortion without the need for surgical intervention (at 24 hours)** 1 day interval: 23/50; 2 day interval: 34/50 **Outcome: Incomplete abortion with the need for surgical intervention** 1 day interval:1/50; 2 day interval: 0/50 **Outcome: Nausea/vomiting** 1 day interval: 14/50; 2 day interval: 15/50 **Outcome: Diarrhoea** 1 day interval: 9/50;	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: low risk, computer-generated random number sequence used for randomization Allocation concealment: unclear risk, not described Blinding of participants and personnel: No blinding; blinding not feasible ,low risk for objective outcomes, high risk for subjective outcomes Blinding of outcome assessment: no blinding; blinding not feasible, low risk for objective outcomes, high risk for subjective outcomes Attrition bias: low risk for critical outcomes, high risk for nausea/vomiting and diarrhoea as the data regarding complications was collected at follow-up and 17/50 from 1 day interval and 15/50 from 2 day interval were lost to follow up, but data for analysis was available for main outcomes

Study details	Participants	Interventions	Outcomes and Results	Comments
and 2 day mifepristone and misoprostol intervals for second trimester termination of pregnancy **Study dates** January 1 to November 30, 2009 **Source of funding** This study was funded by the Science and Technology Commission of the Shanghai Municipality of China (No. 08411966300).	at 13 to 16 weeks of gestation 3) Willing to comply with the schedule of follow-up visits **Exclusion criteria** 1) Contraindications to mifepristone, including adrenal disease or steroid-dependent cancer 2) Contraindications to misoprostol, including glaucoma, blood pressure over 140/90 mm Hg, severe asthma, or known allergy to prostaglandins 3) History or evidence of thromboembolism or severe or recurrent liver disease 4) Known history of or active medical disease 5) History of regular use of prescription drugs		2 day interval: 4/50	Selective reporting: low risk, all outcomes reported in sufficient detail for analysis **Other information** None

Study details	Participants	Interventions	Outcomes and Results	Comments
	6) Intrauterine contraceptive device in utero 7) Haemoglobin level of less than 95 g/L 8) Abnormal liver or renal function tests 9) Breastfeeding 10) Smoking more than 20 cigarettes per day			
Full citation Mentula, M, Suhonen, S, Heikinheimo, O, One- and two-day dosing intervals between mifepristone and misoprostol in second trimester medical termination of pregnancy--a randomized trial, Human reproduction (oxford, England), 26, 2690-2697, 2011 **Ref Id** 816255 **Country/ies where the study was carried out** Finland	**Sample size** n=227 **Characteristics** Age:[years, median (IQR)] 1 day interval: (n = 115): 23 (20 to 27); 2 day interval: (n = 112): 23 (20 to 29) Gestation at termination of pregnancy, days [median (IQR)] 1 day interval (n = 115): 104 (98 to 119); 2 day interval (n = 112): 106 (98 to 122)	**1 day interval:** 200 mg mifepristone oral followed by 400 mcg vaginal misoprostol 20 to 28 hours later and then every 3 hours, for up to 5 doses per 24 hours **2 day interval:** 200 mg mifepristone orally followed by 400 mcg vaginal misoprostol 2 days (40 to 48 hours) later and every 3 hours with up to 5 doses per 24 hours If termination of pregnancy did not occur after 24 hours of administration of the first misoprostol dose, a	**Outcome: Time to expulsion, median (interquartile range)** 1 day interval (n = 115): 8.5 (6.3 to 12.3) hours; 2 day interval (n = 112): 7.2 (5.8 to 9.2) hours **Outcome: Incomplete abortion with the need for surgical intervention** 1 day interval: 29/115; 2 day interval: 41/112 **Outcome: Haemorrhage requiring transfusion or >500ml of blood loss** 1 day interval: 8/115; 2 day interval: 7/112	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: low risk; randomisation using computer-assisted random block system Allocation concealment: low risk; group allocation assignments were kept in sealed, opaque envelopes Blinding of participants and personnel: no blinding; not practical to blind the women and staff ,low risk for objective outcomes, high risk for subjective outcomes Blinding of outcome assessment: no blinding; not feasible to blind; low risk for objective outcomes, high risk for subjective outcomes

Study details	Participants	Interventions	Outcomes and Results	Comments
Study type Randomized controlled trial **Aim of the study** To compare effectiveness of 1 and 2 day intervals between mifepristone and misoprostol in second trimester medical termination of pregnancy **Study dates** 7 May 2008 to 6 July 2010 **Source of funding** Funded by Helsinki University Central Hospital Research funds.	**Inclusion criteria** 1) Age more than or equal to 18 years 2) Viable singleton pregnancy between 13 and 24 weeks of gestation 3) A legal indication for termination of pregnancy 4) Official approval from the Finnish Legal Authority for Medicolegal Affairs as required by Finnish legislation on termination of pregnancy **Exclusion criteria** 1) Allergy to study medication 2) Severe or complicated asthma not responding to medication 3) Suspected ectopic pregnancy, coronary disease or high risk factors for it	transvaginal ultrasonography was done. A second (and third) course of vaginal misoprostol was given if no signs of termination of pregnancy were seen.	**Outcome: Vomiting** Although vomiting is not reported, the need for anti-emetic drugs is reported as an indirect outcome. 1 day interval: 30/115; 2 day interval: 24/112	Attrition bias: low risk for all outcomes; Intention to treat analysis done for all outcomes Selective reporting: low risk; outcomes reported in sufficient detail for analysis **Other information** None

Study details	Participants	Interventions	Outcomes and Results	Comments
	4) Intrauterine contraceptive device in the uterus at the time of termination 5) Lack of a common language with the medical staff			
Full citation Ngai, S. W., Tang, O. S., Ho, P. C., Randomized comparison of vaginal (200 mug every 3 h) and oral (400 mug every 3 h) misoprostol when combined with mifepristone in termination of second trimester pregnancy, Human Reproduction, 15, 2205-2208, 2000 **Ref Id** 771176 **Country/ies where the study was carried out** China **Study type** Randomized controlled trial	**Sample size** n=139 **Characteristics** Age, mean(standard deviation) Oral misoprostol 400 mcg (n=70): 20.4 (4.7) years; Vaginal misoprostol 200 mcg (n=69): 20.2 (4.0) years **Inclusion criteria** 1) Healthy women with age between 16 and 35 years 2) Those requesting legal second trimester termination of pregnancy **Exclusion criteria**	**Oral misoprostol 400 mcg:** 200 mg mifepristone oral followed 36 to 48 hours later by 400 mcg oral misoprostol every 3 hours up to 5 doses + vaginal vitamin B6 placebo **Vaginal misoprostol 200 mcg:** 200 mg mifepristone oral followed 36 to 48 hours later by 200 mcg vaginal misoprostol every 3 hours up to 5 doses + oral vitamin B6 placebo If the women did not abort at 24 hours, a repeat dose of oral misoprostol was given. If there was no response, vaginal gemeprost was administered. In cases of incomplete abortion, evacuation was carried out.	**Outcome: Time to expulsion, mean(standard deviation)** Oral misoprostol 400 mcg (n=70): 20.8 (25.3) hours; Vaginal misoprostol 200 mcg (n=69): 19.5 (34.3) hours **Outcome: Complete abortion without the need for surgical intervention (at 24 hours)** Oral misoprostol 400 mcg: 57/70; Vaginal misoprostol 200 mcg: 58/69 **Outcome: Incomplete abortion with the need for surgical intervention** Oral misoprostol 400 mcg: 0/70; Vaginal misoprostol 200 mcg: 0/69	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: unclear risk, randomization technique not described Allocation concealment: low risk; sealed envelopes with serial numbers in front and allocated grouping inside Blinding of participants and personnel: low risk; blinding not described; placebo used Blinding of outcome assessment: no blinding; blinding not practical, low risk for objective outcomes, high risk for subjective outcomes Attrition bias: low risk for all outcomes; 3 exclusions, with reasons for exclusion reported (1 default to treatment, 1 protocol violation and 1 drug sensitivity). Data on remaining 139/139 subjects reported for all outcomes.

Study details	Participants	Interventions	Outcomes and Results	Comments
Aim of the study To compare the effectiveness of oral misoprostol given 400 mcg every 3 hours to vaginal misoprostol 200 mcg every 3 hours in termination of second trimester pregnancy after 200 mg oral mifepristone **Study dates** Not reported **Source of funding** Not reported	1) Those using prescription drugs regularly 2) women with an intrauterine device 3) Nursing mothers 4) Multiple pregnancies 5) Heavy smokers		**Outcome: Vomiting** Oral misoprostol 400 mcg: 31/70; Vaginal misoprostol 200 mcg: 29/69 **Outcome: Diarrhoea** Oral misoprostol 400 mcg: 28/70; Vaginal misoprostol 200 mcg:16/69	Selective reporting: low risk; all outcomes reported in sufficient detail for analysis **Other information** None
Full citation Tang, O. S., Chan, C. C. W., Kan, A. S. Y., Ho, P. C., A prospective randomized comparison of sublingual and oral misoprostol when combined with mifepristone for medical abortion at 12-20 weeks' gestation, Human Reproduction, 20, 3062-3066, 2005	**Sample size** N=118 **Characteristics** Age, mean (standard deviation): Sublingual misoprostol (n=58): 26.5 (7.6) years; Oral misoprostol (n=60): 24.9 (6.8) years	**Sublingual misoprostol:** 200 mg mifepristone oral followed 36 to 48 hours later by sublingual misoprostol 400 mcg every 3 hours up to 5 doses **Oral misoprostol:** 200 mg oral mifepristone followed 36 to 48 hours later by oral misoprostol 400 mcg every 3 hours up to 5 doses	**Outcome: Time to expulsion, median (range)** Sublingual misoprostol (n=58): 5.5 (1.4 to 43.2) hours; Oral misoprostol (n=60): 7.5 (2.4 to 38.8) hours **Outcome: Complete abortion without the need for surgical intervention (at 48 hours)** Sublingual misoprostol: 57/58;	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: low risk; computer-generated randomization Allocation concealment: low risk; sealed, sequentially numbered treatment packs used for allocation Blinding of participants and personnel: low risk; double blinding

Study details	Participants	Interventions	Outcomes and Results	Comments
Ref Id 816495 **Country/ies where the study was carried out** China **Study type** Randomized controlled trial **Aim of the study** To compare the effectiveness of sublingual to oral misoprostol when used with mifepristone for second trimester medical abortion **Study dates** August 2002 to January 2004 **Source of funding** This research was supported by a grant from the Research Grants Council of the Hong Kong Special Administrative	**Inclusion criteria** 1) Women aged more than 18 years 2) Those requesting legal termination of pregnancy at 12 to 20 weeks of gestation 3) Seeking services at Queen Mary Hospital in Hong Kong during study dates **Exclusion criteria** 1) Women using prescription drugs regularly 2) Women with an intrauterine contraceptive device in utero 3) Nursing mothers 4) Multiple pregnancies 5) Heavy smokers	If termination of pregnancy did not occur after receiving the drug regimen, a second course of 5 doses of misoprostol and placebo was repeated. After the termination of pregnancy, the products of conception were examined and, in case of incomplete abortion i, evacuation of the uterus was done.	Oral misoprostol: 55/60 **Outcome: Incomplete abortion with the need for surgical intervention** Sublingual misoprostol:10/58; Oral misoprostol:7/60 **Outcome: Diarrhoea** Sublingual misoprostol: 8/58; Oral misoprostol:13/60	Blinding of outcome assessment: low risk; blinding of investigators Attrition bias: low risk for all outcomes; 2 exclusions with reasons for exclusion reported (1 participant did not receive the intervention due to abnormal LFT, and the other was allergic to misoprostol). Data on remaining 139/139 subjects reported for all outcomes. Selective reporting: low risk; all outcomes reported in sufficient detail for analysis **Other information** None

Study details	Participants	Interventions	Outcomes and Results	Comments
Region, China (Project No: HKU 7244/01M).				

AMC: Academic Medical Center; ECG: electrocardiogram; HKU: Hong Kong University; IQR: interquartile range; LFT: liver function test; mcg: micrograms; NA: not applicable

Appendix E – Forest plots

Forest plots for review question: What is the optimal regimen and route of administration of misoprostol after mifepristone, for inducing medical termination from 10^{+1} to 24^{+0} weeks?

No meta-analysis was undertaken for this review.

Appendix F – GRADE tables

GRADE tables for review question: What is the optimal regimen and route of administration of misoprostol after mifepristone, for inducing medical termination from 10^{+1} to 24^{+0} weeks?

Table 3: Clinical evidence profile: Comparison 1. 200 mcg versus 400 mcg vaginal misoprostol (at 4 hour intervals) 36 to 48 hours after oral mifepristone 200 mg

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	200 mcg vaginal misoprostol	400 mcg vaginal misoprostol	Relative (95% CI)	Absolute		
Time to expulsion (Better indicated by lower values)												
1 (Browns 2010)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	Median (range) 9.2 (7.1 to 11.3; n=86)	Median (range) 8.0 (7.1 to 8.9; n=90)	Not estimable[2]	Not estimable[2]	LOW	CRITICAL
Complete abortion without the need for surgical intervention (follow-up mean 48 hours)												
1 (Browns 2010)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	57/86 (66.3%)	66/90 (73.3%)	RR 0.9 (0.74 to 1.1)	73 fewer per 1000 (from 191 fewer to 73 more)	LOW	CRITICAL
Incomplete abortion with the need for surgical intervention												
1 (Browns 2010)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	29/86 (33.7%)	24/90 (26.7%)	RR 1.26 (0.8 to 1.99)	69 more per 1000 (from 53 fewer to 264 more)	LOW	CRITICAL
Haemorrhage requiring transfusion or >500 ml of blood loss												
1 (Browns 2010)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	None	4/86 (4.7%)	3/90 (3.3%)	RR 1.4 (0.32 to 6.05)	13 more per 1000 (from 23 fewer to 168 more)	LOW	IMPORTANT
Vomiting												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	200 mcg vaginal misoprostol	400 mcg vaginal misoprostol	Relative (95% CI)	Absolute		
1 (Brouns 2010)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[6]	None	27/86 (31.4%)	37/90 (41.1%)	RR 0.76 (0.51 to 1.14)	99 fewer per 1000 (from 201 fewer to 58 more)	MODERATE	IMPORTANT
Diarrhoea												
1 (Brouns 2010)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	5/86 (5.8%)	10/90 (11.1%)	RR 0.52 (0.19 to 1.47)	53 fewer per 1000 (from 90 fewer to 52 more)	LOW	IMPORTANT

CI: confidence interval; MID: minimally important difference; RR: risk ratio

[1]As this outcome is only reported as medians and ranges for which there are no established or default GRADE MIDs, the imprecision ratings were undertaken by using the optimum information size so that if the total n≥400, then the quality was not downgraded, if n=200-399, then the quality was downgraded by 1 level and if the total n<200, then the quality was downgraded by 2 levels

[2]Cannot be rated/calculated as the study only reports medians and ranges (hours), not means and standard deviations, which were: 200 mcg: Median (range) 9.2 (7.1 to 11.3; n=86); 400 mcg: Median (range) 8.0 (7.1 to 8.9; n=90); p < 0.05 (log rank test)

[3]The MID for this outcome is 3%, and the imprecision ratings were undertaken on that basis by using the absolute effect estimates so that if the CI crosses 30 fewer (3% of 1000) or 30 more, then the quality was downgraded by 1 level. If the CI crosses both, then the quality was downgraded by 2 levels

[4]The quality of evidence was downgraded by 2 levels as the 95% confidence interval crosses 2 MIDs

[5]The MID for this outcome is statistical significance, and the imprecision ratings were undertaken on that basis by using the optimum information size so that if the total event rate ≥300, then the quality was not downgraded, if the event rate = 150-299, then the quality was downgraded by 1 level and if the event rate <150, then the quality was downgraded by 2 levels

[6]The quality of evidence was downgraded by 1 level as the 95% confidence interval crosses 1 MID

Table 4: Clinical evidence profile: Comparison 2. Vaginal versus oral misoprostol (400 mcg, at 3 hour intervals up to 4 doses following a loading dose of vaginal misoprostol 600 mcg) 36 to 48 hours after oral mifepristone 600 mg

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal misoprostol	Oral misoprostol	Relative (95% CI)	Absolute		
Time to expulsion (Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal misoprostol	Oral misoprostol	Relative (95% CI)	Absolute		
1 (El Rafaey 1995)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	35	34	-	MD 0.7 lower (2.03 lower to 0.63 higher)	HIGH	CRITICAL
Complete abortion without the need for surgical intervention (follow-up mean 48 hours)												
1 (El Rafaey 1995)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	34/35 (97.1%)	33/34 (97.1%)	RR 1 (0.92 to 1.09)	0 fewer per 1000 (from 78 fewer to 87 more)	LOW	CRITICAL
Incomplete abortion with the need for surgical intervention												
1 (El Rafaey 1995)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	1/34 (2.9%)	0/35 (0%)	RR 3.09 (0.13 to 73.21)	Not estimable	LOW	CRITICAL
Haemorrhage requiring transfusion or >500 ml of blood loss												
1 (El Rafaey 1995)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	0/35 (0%)	0/34 (0%)	Not estimable	Not estimable	LOW	IMPORTANT
Vomiting												
1 (El Rafaey 1995)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	20/35 (57.1%)	21/34 (61.8%)	RR 0.93 (0.63 to 1.37)	43 fewer per 1000 (from 229 fewer to 229 more)	LOW	IMPORTANT
Diarrhoea												
1 (El Rafaey 1995)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	10/35 (28.6%)	12/34 (35.3%)	RR 0.81 (0.4 to 1.62)	67 fewer per 1000 (from 212 fewer to 219 more)	LOW	IMPORTANT

CI: confidence interval; MD: mean difference; MID: minimally important difference; RR: risk ratio
*[1]MID boundaries -2.18,0.78 (-0.7 +/- 2.95 * 0.5); clinically important effect = 2.95*0.5 = 1.48 higher or lower)*
[2]The MID for this outcome is 3%, and the imprecision ratings were undertaken on that basis by using the absolute effect estimates so that if the CI crosses 30 fewer (3% of 1000) or 30 more, then the quality was downgraded by 1 level. If the CI crosses both, then the quality was downgraded by 2 levels

[3]The quality of evidence was downgraded by 2 levels as the 95% confidence interval crosses 2 MIDs.
[4]The MID for this outcome is statistical significance, and the imprecision ratings were undertaken on that basis by using the optimum information size so that if the total event rate ≥300, then the quality was not downgraded, if the event rate = 150-299, then the quality was downgraded by 1 level and if the event rate <150, then the quality was downgraded by 2 levels

Table 5: Clinical evidence profile: Comparison 3. Vaginal versus oral misoprostol (400 mcg; at 4 hour intervals for vaginal misoprostol and 3 hour intervals for oral misoprostol, up to 5 doses following a loading dose of vaginal misoprostol 800 mcg) 24 to 48 hours after oral mifepristone 200 mg

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal misoprostol 400 mcg	Oral misoprostol 400 mcg	Relative (95% CI)	Absolute		
Time to expulsion (Better indicated by lower values)												
1 (Dickinson 2014)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	Median (range) 7.4 (6.5 to 8.2; n=100)	Median (range) 9.5 (8.5 to 11.4; n=100)	Not estimable[2]	Not estimable[2]	MODERAT	CRITICAL
Haemorrhage requiring transfusion or >500 ml of blood loss												
1 (Dickinson 2014)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	1/100 (1%)	2/100 (2%)	RR 0.5 (0.05 to 5.43)	10 fewer per 1000 (from 19 fewer to 89 more)	LOW	IMPORTANT
Patient satisfaction (opinion of procedure score; Better indicated by lower values)												
1 (Dickinson 2014)	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Serious[1]	None	Median (range) 50 (26 to 50; n=100)	Median (range) 50 (20 to 50; n=100)	Not estimable[5]	Not estimable[5]	LOW	IMPORTANT

CI: confidence interval; MID: minimally important difference; RR: risk ratio
[1]As this outcome is only reported as medians and ranges for which there are no established or default GRADE MIDs, the imprecision ratings were undertaken by using the optimum information size so that if the total n≥400, then the quality was not downgraded, if n=200-399, then the quality was downgraded by 1 level and if the total n<200, then the quality was downgraded by 2 levels
[2]Cannot be rated/calculated as the study only reports medians and ranges (hours), not means and standard deviations, which were: Vaginal misoprostol: Median (range) 7.4 (6.5 to 8.2; n=100); Oral misoprostol: Median (range) 9.5 (8.5 to 11.4; n=100); p < 0.05 (log rank test)
[3]The MID for this outcome is statistical significance, and the imprecision ratings were undertaken on that basis by using the optimum information size so that if the total event rate ≥300, then the quality was not downgraded, if the event rate = 150-299, then the quality was downgraded by 1 level and if the event rate <150, then the quality was downgraded by 2 levels

[4]The quality of evidence was downgraded by 1 level due to serious risk of bias because of lack of blinding for this subjective outcome
[5]Cannot be rated/calculated as the study only reports medians and ranges (opinion of procedure score), not means and standard deviations, which were: Vaginal misoprostol: Median (range) 50 (26 to 50; n=100); Oral misoprostol: Median (range) 50 (20 to 50; n=100); not significant

Table 6: Clinical evidence profile: Comparison 4. Vaginal versus oral misoprostol (200 mcg; at 3 hour intervals, up to 5 doses) ± placebo 36 to 48 hours after 200 mg oral mifepristone

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal misoprostol	Oral misoprostol	Relative (95% CI)	Absolute	Quality	Importance
Time to expulsion (Better indicated by lower values)												
1 (Ho 1997)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	49	49	-	MD 13 lower (23.23 to 2.77 lower)	LOW	CRITICAL
Complete abortion without the need for surgical intervention (follow-up mean 48 hours)												
1 (Ho 1997)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	36/49 (73.5%)	29/49 (59.2%)	RR 1.24 (0.93 to 1.65)	142 more per 1000 (from 41 fewer to 385 more)	LOW	CRITICAL
Vomiting												
1 (Ho 1997)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	14/49 (28.6%)	10/49 (20.4%)	RR 1.4 (0.69 to 2.84)	82 more per 1000 (from 63 fewer to 376 more)	LOW	IMPORTANT
Diarrhoea												
1 (Ho 1997)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	None	9/49 (18.4%)	16/49 (32.7%)	RR 0.56 (0.28 to 1.15)	144 fewer per 1000 (from 235 fewer to 49 more)	MODERATE	IMPORTANT

CI: confidence interval; MD: mean difference; MID: minimally important difference; RR: risk ratio; SD: standard deviation
*[1]The quality of evidence was downgraded by 2 levels as the 95% confidence interval crosses 2 MID (MID boundaries -22.1,-3.9(-13 +/- 18.2 * 0.5); clinically important effect = 18.2*0.5 = 9.1 higher or lower)*

[2]The MID for this outcome is 3%, and the imprecision ratings were undertaken on that basis by using the absolute effect estimates so that if the CI crosses 30 fewer (3% of 1000) or 30 more, then the quality was downgraded by 1 level. If the CI crosses both, then the quality was downgraded by 2 levels[3]The quality of evidence was downgraded by 2 levels as the 95% confidence interval crosses 2 MIDs
[4]The quality of evidence was downgraded by 1 level as the 95% confidence interval crosses 1 MID

Table 7: Clinical evidence profile: Comparison 5. Oral versus vaginal misoprostol (400 mcg at 3 hour intervals, up to 5 doses) ± placebo 36 to 48 hours after oral mifepristone 200 mg

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral misoprostol	Vaginal misoprostol	Relative (95% CI)	Absolute		
Time to expulsion (Better indicated by lower values)												
1 (Ngai 2000)	Randomised trials	Serious [1]	No serious inconsistency	No serious indirectness	No serious imprecision[2]	None	70	69	-	MD 1.3 lower (8.7 lower to 11.33 higher)	MODERATE	CRITICAL
Complete abortion without the need for surgical intervention (follow-up mean 48 hours)												
1 (Ngai 2000)	Randomised trials	Serious [1]	No serious inconsistency	No serious indirectness	Very serious[3]	None	57/70 (81.4%)	58/69 (84.1%)	RR 0.97 (0.83 to 1.13)	25 fewer per 1000 (from 143 fewer to 109 more)	VERY LOW	CRITICAL
Incomplete abortion with the need for surgical intervention												
1 (Ngai 2000)	Randomised trials	Serious [1]	No serious inconsistency	No serious indirectness	Very serious[4]	None	0/70 (0%)	0/69 (0%)	Not estimable	Not estimable	VERY LOW	CRITICAL
Vomiting												
1 (Ngai 2000)	Randomised trials	Serious [1]	No serious inconsistency	No serious indirectness	Very serious[5]	None	31/70 (44.3%)	29/69 (42%)	RR 1.05 (0.72 to 1.54)	21 more per 1000 (from 118 fewer to 227 more)	VERY LOW	IMPORTANT
Diarrhoea												
1 (Ngai 2000)	Randomised trials	Serious [1]	No serious inconsistency	No serious indirectness	Serious[6]	None	28/70 (40%)	16/69 (23.2%)	RR 1.73 (1.03 to 2.89)	169 more per 1000 (from 7	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral misoprostol	Vaginal misoprostol	Relative (95% CI)	Absolute		
										more to 438 more)		

CI: confidence interval; MD: mean difference; MID: minimally important difference; RR: risk ratio
[1]The quality of evidence was downgraded by 1 level due to serious risk of bias arising from unclear method of randomization
*[2]MID boundaries (-18.45,15.85(-1.3 +/- 34.3 * 0.5); clinically important effect = 34.3*0.5 = 17.15 higher or lower)*
[3]The MID for this outcome is 3%, and the imprecision ratings were undertaken on that basis by using the absolute effect estimates so that if the CI crosses 30 fewer (3% of 1000) or 30 more, then the quality was downgraded by 1 level. If the CI crosses both, then the quality was downgraded by 2 levels
[4]The quality of evidence was downgraded by 2 levels due to very serious imprecision because of small number of events
[5]The quality of evidence was downgraded by 2 levels as the 95% confidence interval crosses 2 MIDs
[6]The quality of evidence was downgraded by 1 level as the 95% confidence interval crosses 1 MID

Table 8: Clinical evidence profile: Comparison 6. Sublingual versus oral misoprostol (400 mcg; at 3 hour intervals, up to 5 doses following a loading dose of vaginal misoprostol 800 mcg) 24 to 48 hours after oral mifepristone 200 mg

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sublingual misoprostol	Oral misoprostol	Relative (95% CI)	Absolute		
Time to expulsion (Better indicated by lower values)												
1 (Dickinson 2014)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	Median (range) 7.8 (7 to 9.2 n=102)	Median (range) 9.5 (8.5 to 11.4; n=100)	Not estimable[2]	Not estimable[2]	MODERATE	CRITICAL
Haemorrhage requiring transfusion or >500 ml of blood loss												
1 (Dickinson 2014)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	2/102 (2%)	2/100 (2%)	RR 0.98 (0.14 to 6.83)	0 fewer per 1000 (from 17 fewer to 117 more)	LOW	IMPORTANT
Patient satisfaction (opinion of procedure score; Better indicated by lower values)												
1 (Dickinson 2014)	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Serious[1]	None	Median (range) 50 (19-50; n=102)	Median (range) 50 (20-50; n=100)	Not estimable[5]	Not estimable[5]	LOW	IMPORTANT

CI: confidence interval; MID: minimally important difference; RR: risk ratio
[1]As this outcome is only reported as medians and ranges for which there are no established or default GRADE MIDs, the imprecision ratings were undertaken by using the optimum information size so that if the total n≥400, then the quality was not downgraded, if n=200-399, then the quality was downgraded by 1 level and if the total n<200, then the quality was downgraded by 2 levels
[2]Cannot be rated/calculated as the study only reports medians and ranges (hours), not means and standard deviations, which were: Sublingual misoprostol: Median (range) 7.8 (7 to 9.2; n=102); Oral misoprostol: Median (range) 9.5 (8.5 to 11.4; n=100); p < 0.05 (log rank test)
[3]The MID for this outcome is statistical significance, and the imprecision ratings were undertaken on that basis by using the optimum information size so that if the total event rate ≥300, then the quality was not downgraded, if the event rate = 150-299, then the quality was downgraded by 1 level and if the event rate <150, then the quality was downgraded by 2 levels
[4]The quality of evidence was downgraded by 1 level due to serious risk of bias because of lack of blinding for this subjective outcome
[5]Cannot be rated/calculated as the study only reports medians and ranges (opinion of procedure scores), not means and standard deviations, which were: Sublingual misoprostol: Median (range) 50 (19 to 50; n=102); Oral misoprostol: Median (range) 50 (20 to 50; n=100); not significant

Table 9: Clinical evidence profile: Comparison 7. Sublingual versus oral misoprostol (400 mcg, at 3 hour intervals up to 5 doses) 36 to 48 hours after oral mifepristone 200 mg

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sublingual misoprostol	Oral misoprostol	Relative (95% CI)	Absolute	Quality	Importance
Time to expulsion (Better indicated by lower values)												
1 (Tang 2005)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	Median (range) 5.5 (1.4 to 43.2; n=58)	Median (range) 7.5 (2.4 to 38.8; n=60)	Not estimable[2]	Not estimable[2]	LOW	CRITICAL
Complete abortion without the need for surgical intervention (follow-up mean 48 hours)												
1 (Tang 2005)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	57/58 (98.3%)	55/60 (91.7%)	RR 1.07 (0.99 to 1.17)	64 more per 1000 (from 9 fewer to 156 more)	MODERATE	CRITICAL
Incomplete abortion with the need for surgical intervention												
1 (Tang 2005)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	10/58 (17.2%)	7/60 (11.7%)	RR 1.48 (0.6 to 3.62)	56 more per 1000 (from 47 fewer to 306 more)	LOW	CRITICAL
Diarrhoea												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sublingual misoprostol	Oral misoprostol	Relative (95% CI)	Absolute		
1 (Tang 2005)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	8/58 (13.8%)	13/60 (21.7%)	RR 0.64 (0.29 to 1.42)	78 fewer per 1000 (from 154 fewer to 91 more)	LOW	IMPORTANT

CI: confidence interval; MID: minimally important difference; RR: risk ratio
[1]As this outcome is only reported as medians and ranges for which there are no established or default GRADE MIDs, the imprecision ratings were undertaken by using the optimum information size so that if the total n≥400, then the quality was not downgraded, if n=200-399, then the quality was downgraded by 1 level and if the total n<200, then the quality was downgraded by 2 levels
[2]Cannot be rated/calculated as the study only reports medians and ranges (hours), not means and standard deviations, which were: Sublingual misoprostol: Median (range) 5.5(1.4 to 43.2; n=58); Oral misoprostol: Median (range) 7.5 (2.4 to 38.8; n=100); p < 0.05 (Mann-Whitney U-Test)
[3]The MID for this outcome is 3%, and the imprecision ratings were undertaken on that basis by using the absolute effect estimates so that if the CI crosses 30 fewer (3% of 1000) or 30 more, then the quality was downgraded by 1 level. If the CI crosses both, then the quality was downgraded by 2 levels
[4]The quality of evidence was downgraded by 2 levels as the 95% confidence interval crosses 2 MIDs

Table 10: Clinical evidence profile: Comparison 8. Sublingual (600 mcg; followed by 400 mcg at 3 hour intervals up to 5 doses) versus vaginal (800 mcg; followed by 400 mcg at 3 hour intervals up to 5 doses) misoprostol, 36 to 48 hours after oral mifepristone 200 mg

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sublingual misoprostol	Vaginal misoprostol	Relative (95% CI)	Absolute		
Time to expulsion (Better indicated by lower values)												
1 (Hamoda 2005)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	Median (range) 5.27 (0.55 to 29.35; n=36)	Median (range) 5.40 (2.10 to 13.00; n=40)	Not estimable[2]	Not estimable[2]	LOW	CRITICAL
Incomplete abortion with the need for surgical intervention												
1 (Hamo	Randomised trials	No serious	No serious inconsistency	No serious indirectness	Very serious[3]	None	3/36 (8.3%)	1/40 (2.5%)	RR 3.33 (0.36 to 30.63)	58 more per 1000 (from	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sublingual misoprostol	Vaginal misoprostol	Relative (95% CI)	Absolute		
da 2005)		risk of bias								16 fewer to 741 more)		
Vomiting												
1 (Hamoda 2005)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	25/36 (69.4%)	25/40 (62.5%)	RR 1.11 (0.80 to 1.54)	69 more per 1000 (from 125 fewer to 337 more)	LOW	IMPORTANT
Satisfaction (satisfied with the route of administration of misoprostol)												
1 (Hamoda 2005)	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Very serious[3]	None	24/36 (66.7%)	25/40 (62.5%)	RR 1.07 (0.76 to 1.49)	44 more per 1000 (from 150 fewer to 306 more)	VERY LOW	IMPORTANT
Diarrhoea												
1 (Hamoda 2005)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	19/36 (52.8%)	21/40 (52.5%)	RR 1.01 (0.66 to 1.54)	5 more per 1000 (from 178 fewer to 283 more)	LOW	IMPORTANT

CI: confidence interval; MID: minimally important difference; RR: risk ratio

[1]As this outcome is only reported as medians and ranges for which there are no established or default GRADE MIDs, the imprecision ratings were undertaken by using the optimum information size so that if the total n≥400, then the quality was not downgraded, if n=200-399, then the quality was downgraded by 1 level and if the total n<200, then the quality was downgraded by 2 levels

[2]Cannot be rated/calculated as the study only reports medians and ranges (hours), not means and standard deviations, which were: Sublingual misoprostol: Median (range) 5.27(0.55 to 29.35; n=36); Vaginal misoprostol: Median (range) 5.40 (2.10 to 13.00; n=40); not significant (Mann-Whitney U-Test)

[3]The quality of evidence was downgraded by 2 levels as the 95% confidence interval crosses 2 MIDs

[4]The quality of evidence was downgraded by 1 level due to serious risk of bias because of lack of blinding for this subjective outcome

Table 11: Clinical evidence profile: Comparison 9. Oral misoprostol (400 mcg; every 6 hours, up to 2 doses) 1 versus 2 days after oral mifepristone 200 mg + 600 mcg vaginal misoprostol

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1 day interval	2 day interval	Relative (95% CI)	Absolute		
Time to expulsion (Better indicated by lower values)												
1 (Hou 2010)	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision[2]	None	50	50	-	MD 0.20 (1.25 lower to 1.65 higher)	MODERATE	CRITICAL
Complete abortion without the need for surgical intervention (follow-up mean 24 hours)												
1 (Hou 2010)	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	23/50 (46%)	34/50 (68%)	RR 0.68 (0.47 to 0.97)	18 fewer per 1000 (from 20 fewer to 360 fewer)	LOW	CRITICAL
Incomplete abortion with the need for surgical intervention												
1 (Hou 2010)	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[4]	None	1/50 (2%)	0/50 (0%) 0%	RR 3.00 (0.13 to 71.92)	Not estimable	VERY LOW	CRITICAL
Vomiting (Nausea/Vomiting)												
1 (Hou 2010)	Randomised trials	Very serious[5]	No serious inconsistency	Serious[6]	Very serious[4]	None	14/50 (28%)	15/50 (30%)	RR 0.93 (0.51 to 1.72)	21 fewer per 1000 (from 147 fewer to 216 more)	VERY LOW	IMPORTANT
Diarrhoea												
1 (Hou 2010)	Randomised trials	Very serious[5]	No serious inconsistency	No serious indirectness	Very serious[4]	None	9/50 (18%)	4/50 (8%)	RR 2.25 (0.74 to 6.83)	100 more per 1000 (from 21 fewer to 466 more)	VERY LOW	IMPORTANT

CI: confidence interval; MD: mean difference; MID: minimally important difference; RR: risk ratio

[1]The quality of evidence was downgraded by 1 level due to serious risk of bias arising from unclear allocation concealment method

*[2]MID boundaries (-1.3, 1.7(0.2 +/- 3 * 0.5); clinically important effect = 3*0.5 = 1.5 higher or lower))*

[3]The MID for this outcome is 3%, and the imprecision ratings were undertaken on that basis by using the absolute effect estimates so that if the CI crosses 30 fewer (3% of 1000) or 30 more, then the quality was downgraded by 1 level. If the CI crosses both, then the quality was downgraded by 2 levels

[4]The quality of evidence was downgraded by 2 levels as the 95% confidence interval crosses 2 MIDs

[5]The quality of evidence was downgraded by 2 levels due to very serious risk of bias from unclear allocation concealment method and attrition bias

[6]*The quality of evidence was downgraded by 1 level due to indirectness of outcome reported as all cases of nausea and vomiting, instead of vomiting alone*

Table 12: Clinical evidence profile: Comparison 10. Vaginal misoprostol (400 mcg; at 3 hour intervals, up to 5 doses per 24 hours) 1 versus 2 days after oral mifepristone 200 mg

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1 day interval	2 day interval	Relative (95% CI)	Absolute		
Time to expulsion (Better indicated by lower values)												
1 (Mentula 2011)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	Median (range) 8.5 (6.3 to 12.3; n=115)	Median (range) 7.2 (5.8 to 9.2; n=112)	Not estimable[2]	Not estimable[2]	MODERATE	CRITICAL
Incomplete abortion with the need for surgical intervention												
1 (Mentula 2011)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	29/115 (25.2%)	41/112 (36.6%)	RR 0.69 (0.46 to 1.03)	113 fewer per 1000 (from 198 fewer to 11 more)	MODERATE	CRITICAL
Haemorrhage requiring transfusion or >500 ml of blood loss												
1 (Mentula 2011)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	8/115 (7%)	7/112 (6.3%)	RR 1.11 (0.42 to 2.97)	7 more per 1000 (from 36 fewer to 123 more)	LOW	IMPORTANT
Vomiting (The need for anti-emetic drugs)												
1 (Mentula 2011)	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[5]	Very serious[6]	None	30/115 (26.1%)	24/112 (21.4%)	RR 1.22 (0.76 to 1.95)	47 more per 1000 (from 51 fewer to 204 more)	VERY LOW	IMPORTANT

CI: confidence interval; MID: minimally important difference; RR: risk ratio

[1]*As this outcome is only reported as medians and ranges for which there are no established or default GRADE MIDs, the imprecision ratings were undertaken by using the optimum information size so that if the total n≥400, then the quality was not downgraded, if n=200-399, then the quality was downgraded by 1 level and if the total n<200, then the quality was downgraded by 2 levels*

[2]*Cannot be rated/calculated as the study only reports medians and ranges (hours), not means and standard deviations, which were: 1 day interval: Median (range) 8.5 (6.3 to 12.3; n=115); 2 day interval: Median (range)= 7.2 (5.8 to 9.2;n=112); p<0.05 (Mann-Whitney U-Test)*

[3]*The quality of evidence was downgraded by 1 level as the 95% confidence interval crosses 1 MID*

[4]The MID for this outcome is statistical significance, and the imprecision ratings were undertaken on that basis by using the optimum information size so that if the total event rate ≥300, then the quality was not downgraded, if the event rate = 150-299, then the quality was downgraded by 1 level and if the event rate <150, then the quality was downgraded by 2 levels
[5]The quality of evidence was downgraded by 1 level due to indirectness of outcome reported as women needing anti-emetic drugs instead of those experiencing vomiting
[6]The quality of evidence was downgraded by 2 levels as the 95% confidence interval crosses 2 MIDs

Table 13: Clinical evidence profile: Comparison 11. Vaginal misoprostol (600 mcg; followed by 400 mcg at 3 hour intervals, up to 4 doses) simultaneous with mifepristone 200 mg versus 36 to 38 hours after 200 mg oral mifepristone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Simultaneous administration	36 to 38 hours interval	Relative (95% CI)	Absolute		
Time to expulsion (Better indicated by lower values)												
1 (Chai 2009)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	Median (range) 10.0 (3.5 to 126; n=71)	Median (range) 4.9 (1.8 to 13.8; n=70)	Not estimable[2]	Not estimable[2]	LOW	CRITICAL
Complete abortion without the need for surgical intervention (follow-up mean 48 hours)												
1 (Chai 2009)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	70/71 (98.6%)	70/70 (100%)	RR 0.99 (0.95 to 1.03)	10 fewer per 1000 (from 50 fewer to 30 more)	LOW	CRITICAL
Incomplete abortion with the need for surgical intervention												
1 (Chai 2009)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	5/71 (7%)	1/70 (1.4%)	RR 4.93 (0.59 to 41.13)	56 more per 1000 (from 6 fewer to 573 more)	LOW	CRITICAL
Haemorrhage requiring transfusion or >500 ml of blood loss												
1 (Chai 2009)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	None	0/71 (0%)	0/70 (0%)	Not estimable	Not estimable	LOW	IMPORTANT
Diarrhoea (>3 episodes)												
1 (Chai 2009)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[6]	None	18/71 (25.4%)	10/70 (14.3%)	RR 1.77 (0.88 to 3.57)	110 more per 1000 (from 17	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Simultaneous administration	36 to 38 hours interval	Relative (95% CI)	Absolute		
										fewer to 367 more)		

CI: confidence interval; MID: minimally important difference; RR: risk ratio

[1]As this outcome is only reported as medians and ranges for which there are no established or default GRADE MIDs, the imprecision ratings were undertaken by using the optimum information size so that if the total n≥400, then the quality was not downgraded, if n=200-399, then the quality was downgraded by 1 level and if the total n<200, then the quality was downgraded by 2 levels

[2]Cannot be rated/calculated as the study only reports medians and ranges (hours), not means and standard deviations, which were: Simultaneous administration: Median (range) 10.0 (3.5 to 126; n=71); 36 to 38 hours interval: Median (range) 4.9 (1.8 to 13.8; n=70); p<0.0001 (Mann-Whitney U-Test)

[3]The MID for this outcome is 3%, and the imprecision ratings were undertaken on that basis by using the absolute effect estimates so that if the CI crosses 30 fewer (3% of 1000) or 30 more, then the quality was downgraded by 1 level. If the CI crosses both, then the quality was downgraded by 2 levels

[4]The quality of evidence was downgraded by 2 levels as the 95% confidence interval crosses 2 MIDs

[5]The MID for this outcome is statistical significance, and the imprecision ratings were undertaken on that basis by using the optimum information size so that if the total event rate ≥300, then the quality was not downgraded, if the event rate = 150-299, then the quality was downgraded by 1 level and if the event rate <150, then the quality was downgraded by 2 levels

[6]The quality of evidence was downgraded by 1 level as the 95% confidence interval crosses 1 MID

Table 14: Clinical evidence profile: Comparison 12. Buccal misoprostol 400 mcg (at 3 hour intervals) ± placebo simultaneous with mifepristone 200 mg versus 1 day following oral mifepristone 200 mg

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Simultaneous administration	1 day interval	Relative (95% CI)	Absolute		
Time to expulsion (Better indicated by lower values)												
1 (Abbas 2016)	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision[2]	None	Median (range) 13.0 (4.9 to 47.8; n=254)	Median (range) 7.7 (2.1 to 40.3; n=251)	Not estimable [3]	Not estimable[3]	MODERATE	CRITICAL
Complete abortion without the need for surgical intervention(at 48 hours)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Simultaneous administration	1 day interval	Relative (95% CI)	Absolute		
1 (Abbas 2016)	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[4]	None	243/254 (95.7%)	243/251 (96.8%)	RR 0.99 (0.95 to 1.02)	10 fewer per 1000 (from 48 fewer to 19 more)	LOW	CRITICAL
Incomplete abortion with the need for surgical intervention												
1 (Abbas 2016)	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[5]	None	2/254 (0.79%)	1/251 (0.4%)	RR 1.98 (0.18 to 21.66)	4 more per 1000 (from 3 fewer to 82 more)	VERY LOW	CRITICAL
Haemorrhage requiring transfusion or >500 ml of blood loss												
1 (Abbas 2016)	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[6]	None	1/254 (0.39%)	0/251 (0%)	RR 2.96 (0.12 to 72.43)	Not estimable	VERY LOW	IMPORTANT
Vomiting												
1 (Abbas 2016)	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[5]	None	63/254 (24.8%)	57/251 (22.7%)	RR 1.09 (0.8 to 1.49)	20 more per 1000 (from 45 fewer to 111 more)	VERY LOW	IMPORTANT
Patient satisfaction (satisfied or very satisfied)												
1 (Abbas 2016)	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	252/254 (99.2%)	249/251 (99.2%)	RR 1 (0.98 to 1.02)	0 fewer per 1000 (from 20 fewer to 20 more)	MODERATE	IMPORTANT
Diarrhoea												
1 (Abbas 2016)	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	137/254 (53.9%)	83/251 (33.1%)	RR 1.63 (1.32 to 2.01)	208 more per 1000 (from 106 more to 334 more)	MODERATE	IMPORTANT

CI: confidence interval; MID: minimally important difference; RR: risk ratio

[1]The quality of evidence was downgraded by 2 levels due to serious risk of bias arising from unclear randomization methods

[2]As this outcome is only reported as medians and ranges for which there are no established or default GRADE MIDs, the imprecision ratings were undertaken by using the optimum information size so that if the total n≥400, then the quality was not downgraded, if n=200-399, then the quality was downgraded by 1 level and if the total n<200, then the quality was downgraded by 2 levels

[3]Cannot be rated/calculated as the study only reports medians and ranges (hours), not means and standard deviations, which were: Simultaneous administration: Median (range) 13.0 (4.9 to 47.8; n=254); 1 day interval: Median (range) 7.7 (2.1 to 40.3); n=251); p<0.001 (Mann-Whitney U-test)

[4]The MID for this outcome is 3%, and the imprecision ratings were undertaken on that basis by using the absolute effect estimates so that if the CI crosses 30 fewer (3% of 1000) or 30 more, then the quality was downgraded by 1 level. If the CI crosses both, then the quality was downgraded by 2 levels
[5]The quality of evidence was downgraded by 2 levels as the 95% confidence interval crosses 2 MIDs
[6]The MID for this outcome is statistical significance, and the imprecision ratings were undertaken on that basis by using the optimum information size so that if the total event rate ≥300, then the quality was not downgraded, if the event rate = 150-299, then the quality was downgraded by 1 level and if the event rate <150, then the quality was downgraded by 2 levels

Appendix G – Economic evidence study selection

Economic evidence for review question: What is the optimal regimen and route of administration of misoprostol after mifepristone, for inducing medical termination from 10^{+1} to 24^{+0} weeks?

No economic evidence was identified which was applicable to this review question.

Appendix H – Economic evidence tables

Economic evidence tables for review question: What is the optimal regimen and route of administration of misoprostol after mifepristone, for inducing medical termination from 10^{+1} to 24^{+0} weeks?

No economic evidence was identified which was applicable to this review question.

Appendix I –Economic evidence profiles

Economic evidence profiles for review question: What is the optimal regimen and route of administration of misoprostol after mifepristone, for inducing medical termination from 10^{+1} to 24^{+0} weeks?

No economic evidence was identified which was applicable to this review question.

Appendix J –Economic analysis

Economic analysis for review question: What is the optimal regimen and route of administration of misoprostol after mifepristone, for inducing medical termination from 10^{+1} to 24^{+0} weeks?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded studies for review question: What is the optimal regimen and route of administration of misoprostol after mifepristone, for inducing medical termination from 10^{+1} to 24^{+0} weeks?

Clinical studies

Study	Reason for Exclusion
Agrawal, S., Misoprostol for second trimester medical abortion - a comparison of three routes of administration, International journal of gynaecology and obstetrics, 107, 2009	Mifepristone is not included in this regimen
Al, R. A., Yapca, O. E., Vaginal misoprostol compared with buccal misoprostol for termination of second-trimester pregnancy, Obstetrics and gynecology, 126, 593-598, 2015	Mifepristone is not included in this regimen
Azra, B, Shakeel, S, Nilofer, M, A comparison of two protocols of intra vaginal misoprostol for second trimester medical termination of pregnancy, Pakistan armed forces medical journal, 57, 61-65, 2007	Mifepristone is not included in this regimen
Bebbington,M.W., Kent,N., Lim,K., Gagnon,A., Delisle,M.F., Tessier,F., Wilson,R.D., A randomized controlled trial comparing two protocols for the use of misoprostol in midtrimester pregnancy termination, American Journal of Obstetrics and Gynecology, 187, 853-857, 2002	Mifepristone not included in this regimen
Behrashi, M., Mahdian, M., Vaginal versus oral misoprostol for second-trimester pregnancy termination: A randomized trial, Pakistan Journal of Biological Sciences, 11, 2505-2508, 2008	Mifepristone is not included in this regimen
Bhattacharjee, N., Saha, S. P., Ganguly, R. P., Patra, K. K., Jha, T., Barui, G., Saha, M., A randomized comparative study on vaginal administration of acetic acid-moistened versus dry misoprostol for mid-trimester pregnancy termination, Archives of gynecology and obstetrics, 285, 311-316, 2012	Mifepristone is not included in this regimen
Bhattacharjee, N., Saha, S. P., Ghoshroy, S. C., Bhowmik, S., Barui, G., A randomised comparative study on sublingual versus vaginal administration of misoprostol for termination of pregnancy between 13 to 20 weeks, Australian and New Zealand Journal of Obstetrics and Gynaecology, 48, 165-171, 2008	Mifepristone is not included in this regimen
Bhattacharyya, S. K., Mukherji, J., Kamilya, G. S., Ray, S., Hazra, A., Two regimens of vaginal misoprostol in second trimester termination of pregnancy: a prospective randomised trial, Acta obstetricia ET gynecologica scandinavica, 85, 1458-62, 2006	Mifepristone is not included in this regimen
Cabrera, Y., FernUndez-Guisasola, J., Lobo, P., G. Umir S, Ulvarez, J., Comparison of sublingual versus vaginal misoprostol for second-trimester pregnancy termination: A meta-analysis,	Mifepristone is not included in the regimen of studies included in this meta-analysis

Study	Reason for Exclusion
Australian and New Zealand Journal of Obstetrics and Gynaecology, 51, 158-165, 2011	
Caliskan, E., Dilbaz, S., Doger, E., Ozeren, S., Dilbaz, B., Erratum: Randomized comparison of 3 misoprostol protocols for abortion induction at 13-20 weeks of gestation (Journal of Reproductive Medicine (2005) 50 (173-180)), Journal of reproductive medicine for the obstetrician and gynecologist, 50, 732, 2005	This article is an erratum for another excluded study (Caliskan 2005)
Caliskan, E., Dilbaz, S., Doger, E., Ozeren, S., Dilbaz, B., Randomized comparison of 3 misoprostol protocols for abortion induction at 13-20 weeks of gestation, Journal of reproductive medicine for the obstetrician and gynecologist, 50, 173-180, 2005	Mifepristone is not included in this regimen
Caliskan, E., Doger, E., Cakiroglu, Y., Corakci, A., Yucesoy, I., Sublingual misoprostol 100 microgram versus 200 microgram for second trimester abortion: a randomised trial, European Journal of Contraception and Reproductive Health Care, 14, 55-60, 2009	Mifepristone is not included in this regimen
Carbonell, J. L., Torres, M. A., Reyes, R., Ortega, L., Garcia-Gallego, F., Sanchez, C., Second-trimester pregnancy termination with 600-mug vs. 400-mug vaginal misoprostol and systematic curettage postexpulsion: a randomized trial, Contraception, 77, 50-55, 2008	Mifepristone is not included in this regimen
Cetin, C., Buyukkurt, S., Seydaoglu, G., Kahveci, B., Soysal, C., Ozgunen, F. T., Comparison of two misoprostol regimens for mid-trimester pregnancy terminations after FIGO's misoprostol dosage recommendation in 2012, Journal of Maternal-Fetal & Neonatal MedicineJ Matern Fetal Neonatal Med, 29, 1314-7, 2016	Not a randomised controlled trial
Chaudhuri, S., Banerjee, P. K., Mundle, M., Mitra, S. N., A comparison of two regimens of misoprostol for second trimester medical termination of pregnancy: A randomized trial, Tropical doctor, 40, 144-148, 2010	Mifepristone is not included in this regimen
Chen,Q.J., Zhang,J., Huang,Z.R., Fan,X.F., Wang,H.Y., Zhu,H., Hou,S.P., Liu,Y.H., Qiao,Q.Q., Zhang,P., Liu,Y., Qian,C.M., Tan,Y.D., Li,A.H., Meads,C., Zhang,W.H., Cheng,L.N., Mifepristone in combination with misoprostol for the termination of pregnancy at 8-16 weeks' gestational age: A multicentre randomized controlled trial, Journal of Reproduction and Contraception, 24, 101-113, 2013	Mixed population of first and second trimester (period of gestation 8 to16 weeks), with a total of n=1112 of whom n=669 were the target population. Results for this subgroup could not be extracted.
Chen,Q.J., Hou,S.P., Meads,C., Huang,Y.M., Hong,Q.Q., Zhu,H.P., Cheng,L.N., Mifepristone in combination with prostaglandins for termination of 10-16 weeks gestation: A systematic review, European Journal of Obstetrics Gynecology and Reproductive Biology, 159, 247-254, 2011	Systematic review with English and Chinese studies including comparison of different regimens of mifepristone with prostaglandins for termination of pregnancy. Relevant studies are included individually in the current review.

Study	Reason for Exclusion
Cheng, L, Termination of 10-16 weeks' gestation with mifepristone plus misoprostol: a multicentre randomized clinical trial, Zhonghua fu chan ke za zhi, 34, 268-271, 1999	Full text not written in English
Crane, J. M., Young, D., Butt, K., Delaney, M., Hutchens, D., Carlan, S. J., Safety and efficacy of misoprostol orally and vaginally: A randomized trial [3], Obstetrics and gynecology, 98, 875-876, 2001	Letter to Editor
Dalenda,C., Ines,N., Fathia,B., Malika,A., Bechir,Z., Ezzeddine,S., Hela,C., Badis,C.M., Two medical abortion regimens for late first-trimester termination of pregnancy: a prospective randomized trial, Contraception, 81, 323-327, 2010	First trimester termination of pregnancy
Dickinson, J. E., Evans, S. F., A comparison of oral misoprostol with vaginal misoprostol administration in second-trimester pregnancy termination for fetal abnormality, Obstetrics and gynecology, 101, 1294-1299, 2003	Mifepristone is not included in this regimen
Dickinson, J. E., Evans, S. F., The optimization of intravaginal misoprostol dosing schedules in second-trimester pregnancy termination, American journal of obstetrics and gynecology, 186, 470-474, 2002	Mifepristone is not included in this regimen
Ellis, S. C., Kapp, N., Vragpvoc, O., Borgata, L., Randomized trial of buccal versus vaginal misoprostol for induction of second trimester abortion, Contraception, 81, 441-445, 2010	Mifepristone is not included in this regimen
Eslamian, L, Gosili, R, Jamal, A, Alyassin, A, A prospective randomized controlled trial of two regimens of vaginal misoprostol in second trimester termination of pregnancy, Acta medica iranica, 45, 497-500, 2007	Mifepristone is not included in this regimen
Feldman, D. M., Borgida, A. F., Rodis, J. F., Leo, M. V., Campbell, W. A., A randomized comparison of two regimens of misoprostol for second-trimester pregnancy termination, American journal of obstetrics and gynecology, 189, 710-713, 2003	Mifepristone is not included in this regimen
Gilbert, A., Reid, R., A randomised trial of oral versus vaginal administration of misoprostol for the purpose of mid-trimester termination of pregnancy, Australian and New Zealand Journal of Obstetrics and Gynaecology, 41, 407-410, 2001	Mifepristone is not included in this regimen
Gomez Ponce de Leon, R., Wing, D. A., Misoprostol for termination of pregnancy with intrauterine fetal demise in the second and third trimester of pregnancy - a systematic review, Contraception, 79, 259-71, 2009	Systematic review including second and third trimester termination of pregnancy and regimen does not include mifepristone
Guix, C, Palacio, M, Figueras, F, Bennasar, M, Zamora, L, Coll, O, Efficacy of two regimens of misoprostol for early second-trimester pregnancy termination, Fetal diagnosis and therapy, 20, 544-548, 2005	Mifepristone is not included in this regimen

Study	Reason for Exclusion
Guo, Q., Qian, Z., Huang, L., Two cervical preparation regimens prior to surgical abortion at 10-14 weeks of gestation: A randomized clinical trial, Journal of Maternal-Fetal and Neonatal Medicine, 30, 2686-2689, 2017	Mifepristone is not included in this regimen
Heikinheimo, O., Suhonen, S., Haukkamaa, M., One- and 2-day mifepristone-misoprostol intervals are both effective in medical termination of second-trimester pregnancy, Reproductive BioMedicine Online, 8, 236-9, 2004	Not a randomised controlled trial
Herabutya,Y., Chanarachakul,B., Punyavachira,P., Induction of labor with vaginal misoprostol for second trimester termination of pregnancy in the scarred uterus, International Journal of Gynaecology and Obstetrics, 83, 293-297, 2003	Mifepristone is not included in this regimen
Jain, J. K., Kuo, J., Mishell, D. R., Jr., A comparison of two dosing regimens of intravaginal misoprostol for second-trimester pregnancy termination, Obstetrics and Gynecology, 93, 571-575, 1999	Mifepristone is not included in this regimen
Jyothi, S, Pallavi, Mnv, Medical abortion by mifepristone with oral versus vaginal misoprostol, 56, 529-531, 2006	Includes only first trimester pregnancies
Kapp,N., Borgatta,L., Stubblefield,P., Vragovic,O., Moreno,N., Mifepristone in second-trimester medical abortion: a randomized controlled trial, Obstetrics and Gynecology, 110, 1304-1310, 2007	Comparison of mifepristone versus digoxin
Karsidag,A.Y.K., Buyukbayrak,E.E., Kars,B., Dansuk,R., Unal,O., Turan,M.C., Vaginal versus sublingual misoprostol for second-trimester pregnancy termination and effect on Doppler measurements, International Journal of Gynecology and Obstetrics, 106, 250-253, 2009	Mifepristone is not included in this regimen
Khazardoost, S., Hantoushzadeh, S., Madani, M. M., A randomised trial of two regimens of vaginal misoprostol to manage termination of pregnancy of up to 16 weeks, Australian and New Zealand Journal of Obstetrics and Gynaecology, 47, 226-229, 2007	Mifepristone is not included in this regimen
Kurshid, R., Ahmed, A., Mir, S., Ul Shamas, I., To assess the efficacy of two regimens of misoprostol for second trimester pregnancy termination-a randomized comparison, Internet journal of gynecology and obstetrics, 14, 2010	Mifepristone is not included in this regimen
Mahjabeen,, Khawaja, N. P., Rehman, R., Comparison of oral versus vaginal misoprostol for mid-trimester pregnancy termination, Jcpsp, Journal of the College of Physicians & Surgeons - Pakistan, 19, 359-62, 2009	Mifepristone is not included in this regimen
Milani, F., Sharami, S. H., Arjmandi, S., Comparison of sublingual and vaginal misoprostol for second-trimester pregnancy	Mifepristone is not included in this regimen

Study	Reason for Exclusion
terminations, Journal of family and reproductive health, 8, 41-44, 2014	
Nct,, A Comparison of Sublingual and Buccal Misoprostol Regimens After Mifepristone for Mid-trimester Abortion, Https://clinicaltrials.gov/show/nct02708446, 2016	This is a clinical trial record, without details of the study
Nct,, Comparison of Two Regimens of Misoprostol for Second Trimester Medical Termination of Pregnancy, Https://clinicaltrials.gov/show/nct00401440, 2006	This is a clinical trial record, without details of the study
Nct,, Misoprostol for Second Trimester Termination of Pregnancy, Https://clinicaltrials.gov/show/nct00945997, 2009	This is a clinical trial record, without details of the study
Nigam, A., Singh, V. K., Prakash, A., Vaginal vs. oral misoprostol for mid-trimester abortion, International Journal of Gynecology and Obstetrics, 92, 270-271, 2006	Mifepristone is not included in this regimen
Ozerkan, K., Ocakoglu, G., Rehimli, S., Uncu, G., Develioglu, O., A comparison of low-dose and high-dose protocols of vaginal misoprostol for second trimester termination of pregnancy, Clinical and Experimental Obstetrics and Gynecology, 36, 245-247, 2009	Mifepristone is not included in this regimen
Rahimi-Sharbaf, F., Adabi, K., Valadan, M., Shirazi, M., Nekuie, S., Ghaffari, P., Khansari, N., The combination route versus sublingual and vaginal misoprostol for the termination of 13 to 24 week pregnancies: A randomized clinical trial, Taiwanese Journal of Obstetrics and Gynecology, 54, 660-665, 2015	Mifepristone is not included in this regimen
Roy, G, Ferreira, E, Hudon, L, Marquette, G, The efficacy of oral versus vaginal misoprostol for second-trimester termination of pregnancy: a double-blind, randomized, placebo controlled trial, American journal of obstetrics and gynecology, 189, S70, 2003	Mifepristone is not included in this regimen
Saha,S., Bal,R., Ghosh,S., Krishnamurthy,P., Medical abortion in late second trimester - A comparative study with misoprostol through vaginal versus oral followed by vaginal route, Journal of the Indian Medical Association, 104, 81-84, 2006	Mifepristone is not included in this regimen
Shaheen, S., Khattak, N. N., Parveen, T., The use of vaginal misoprostol to terminate the pregnancy in second trimester, Medical Forum Monthly, 25, 20-2, 2014	Mifepristone is not included in this regimen
Shaw, K. A., Topp, N. J., Shaw, J. G., Blumenthal, P. D., Mifepristone-misoprostol dosing interval and effect on induction abortion times: a systematic review, Obstetrics & GynecologyObstet Gynecol, 121, 1335-47, 2013	Systematic review including comparison of different regimens of mifepristone and misoprostol dosing interval. Relevant studies are included individually in the current review.
Tang, O. S., Lau, W. N., Chan, C. C., Ho, P. C., A prospective randomised comparison of	Mifepristone is not included in this regimen

Study	Reason for Exclusion
sublingual and vaginal misoprostol in second trimester termination of pregnancy, 111, 1001-5, 2004	
Tang, O. S., Lee, S. W. H., Ho, P. C., A prospective randomized study on the measured blood loss in medical termination of early pregnancy by three different misoprostol regimens after pretreatment with mifepristone, Human Reproduction, 17, 2865-2868, 2002	Includes pregnancies in first trimester only
Tanha, F. D., Golgachi, T., Niroomand, N., Ghajarzadeh, M., Nasr, R., Sublingual versus vaginal misoprostol for second trimester termination: A randomized clinical trial, Archives of Gynecology and Obstetrics, 287, 65-69, 2013	Mifepristone is not included in this regimen
Von Hertzen, H., Piaggio, G., Wojdyla, D., Huong, N. T. M., Marions, L., Okoev, G., Khomassuridze, A., Kereszturi, A., Mittal, S., Nair, R., Daver, R., Pretnar-Darovec, A., Dickson, K., Hinh, N. D., Bao, N. H., Tuyet, H. T. D., Peregoudov, A., Comparison of vaginal and sublingual misoprostol for second trimester abortion: Randomized controlled equivalence trial, Human Reproduction, 24, 106-112, 2009	Mifepristone is not included in this regimen
Wang, Z, Zheng, Jq, Lin, Xh, Comparison of 3 methods of induction delivery for terminating midtrimester pregnancy of ulterus with scar, 17, 189-190, 2008	Full text not written in English
Webster, D., Penney, G. C., Templeton, A., A comparison of 600 and 200 mg mifepristone prior to second trimester abortion with the prostaglandin misoprostol, British Journal of Obstetrics and Gynaecology, 103, 706-709, 1996	Includes comparison of mifepristone doses, with similar misoprostol regimen for both groups.
Wong, K. S., Ngai, C. S. W., Yeo, E. L. K., Tang, L. C. H., Ho, P. C., A comparison of two regimens of intravaginal misoprostol for termination of second trimester pregnancy: A randomized comparative trial, Human Reproduction, 15, 709-712, 2000	Mifepristone is not included in this regimen
Yazdani, S. H., Zeinalzadeh, M., Bouzari, Z., Golsorkhtabar-Amiri, M., Effects of vaginal versus oral misoprostol to terminate second-trimester pregnancy, Clinical and Experimental Obstetrics and Gynecology, 39, 529-531, 2012	Mifepristone is not included in this regimen

Economic studies

No economic evidence was identified for this review. See supplementary material 2 for further information.

Appendix L – Research recommendations

No research recommendations were made for this review.