Essential Medicines List Application
Mifepristone–Misoprostol for Medical Abortion

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1. Summary statement of the proposal for inclusion, change or deletion

In 2005, mifepristone and misoprostol were included in the Model List of Essential Medicines in the *14th edition (in section 22.1, Oxytocics),* because of their proven safety and efficacy for medical abortion. At that time, given limited available clinical evidence, these medications were added to the Complementary list of EML and included a specific requirement for specialized medical care and direct supervision.

Since this initial EML listing, numerous clinical and programmatic studies as well as systematic reviews have documented the safe and effective provision of mifepristone-misoprostol for medical abortion without the need for specialized medical care and direct supervision. (1-3) WHO guidelines have been updated to reflect this evidence and now state that mifepristone-misoprostol for medical abortion can be safely and effectively offered to pregnant persons without these extra provisions. (1-3)

In the following application, we provide evidence-base justification to support four specific changes in the EML listing pertaining to provision of mifepristone-misoprostol medical abortion.

These proposed changes are to:

1. Move mifepristone-misoprostol from the Complementary to Core Model List of Essential Medicines
2. Remove the asterisk that states that close medical supervision is required for administration of mifepristone-misoprostol for medical abortion
3. Include dosage form for combi-pack[1] containing: mifepristone 200 milligram tablet [1] and misoprostol 200 microgram tablet [4]
4. Remove the statement "Where permitted under national law and where culturally acceptable"

Medical abortion has revolutionized access to safe and effective abortion care globally. Among the hundreds of studies, a large systematic review published in 2013 examined mifepristone-misoprostol medical abortion provision to more than 45,000 women across a range of settings over two decades emphasized that fewer than 5% required surgery to complete termination of pregnancy and the proportion of women with ongoing pregnancy at follow-up was 1.1%. (4) Serious complications requiring hospitalization or blood transfusion occurred in less than 0.4% of women. (4) Studies have also demonstrated that home administration of misoprostol does not increase rates of abortion failure or serious complications. (2-8) The option to self-administer misoprostol has also been found to be highly acceptable to users. (2-8) Finally, evidence supports that there is no medical need for mandatory routine follow-up but that follow-up should be made available if desired by the person. (2, 5) Service delivery with limited

[1] Throughout this application we use the term "combi-pack" to refer to co-packaged mifepristone (1 tablet) and misoprostol (4 tablets) for medical abortion. Other terms used include composite package, co-packaged and combination packs.

medical supervision can improve privacy, convenience and acceptability of the abortion process without compromising safety and effectiveness.

Evidence from WHO guidelines, systematic reviews, hundreds of randomized controlled trials and comparative clinical trials since 2005, support the safety of medical abortion provision at all levels of the health care system. Specifically this means that the continuum of abortion care (pre-abortion care, provision of abortion and follow-up) can be provided in an outpatient setting by various cadres of health workers and is not restricted to specialist doctors. This includes auxiliary nurses/ANMs, nurses, midwives, associate/advanced associate clinicians and non-specialist doctors. (3, 9)

In light of the existing body of evidence supporting its safe and effective use, it is timely that mifepristone-misoprostol be reclassified as Core essential medicines on the Model List of Essential Medicines. Misoprostol is already listed as a Core essential medication for its incomplete abortion, labor induction and PPH indications. By moving mifepristone-misoprostol to the Core list, the WHO will highlight to WHO Member States that these drugs meet the standards of core essential medications meaning that they do not require specialized diagnostic or monitoring facilities and/or specialist care and/or training. (2, 3) Table 1 below highlights the EML listing by year of mifepristone-misoprostol and misoprostol.

Table 1. EML listing, by year

2005	**Misoprostol for labor induction** • Complementary list • *Expert Committee noted "for use for induction of labour where appropriate facilities are available."*	14th Expert Committee on the Selection and Use of Essential Medicines
2005	**Mifepristone +misoprostol for medical abortion** • Complementary list • *Expert Committee noted "requires close medical supervision"* • *Listing includes box stating "where permitted under national law and where culturally acceptable"*	14th Expert Committee on the Selection and Use of Essential Medicines
2010	**Misoprostol for incomplete abortion/management of miscarriage** • Complementary list	17th Expert Committee on the Selection and Use of Essential Medicines
2011	**Misoprostol for prevention of PPH** • *Moved from the Complementary to the Core list* • *Expert Committee added for use "in settings where parenteral uterotonics are not available or feasible."*	18th Expert Committee on the Selection and Use of Essential Medicines
2015	Misoprostol for treatment of PPH • *Core list* • *Expert Committee noted "Prevention and treatment of postpartum haemorrhage where oxytocin is not available or cannot be safely used."*	19th Expert Committee on the Selection and Use of Essential Medicines

This proposal is based on the following evidence and considerations:

1. Mifepristone and misoprostol are safe. The drugs have been used in over 1000 studies since the early 90's and have excellent safety records. (10, 11)
2. Mifepristone-misoprostol medical abortion is highly effective. Clinical studies report successful abortion rates up to 98% with continuing pregnancy occurring in approximately 2% of cases. (1, 2, 4)
3. Since the initial WHO Model List for Essential Medicines application in 2005, l WHO guidelines have been updated to reflect available safety and efficacy data and, in turn, provided guidance for less specialized care in its use. For this reason, the current listing of mifepristone-misoprostol on the Complementary list is out-of-date. Relevant WHO guidelines include:
    - 2012 "Safe Abortion Technical and Policy Guidance" which indicates that in person clinical follow-up visits are not clinically necessary for all patients. (2)
    - 2015 WHO guideline on "Health worker roles in providing safe abortion care and post-abortion contraception" which supports task shifting and task sharing among a wide range of health workers who can safely provide medical abortion with these medications. (3)
    - 2018 Forthcoming WHO guideline on "Medical management of abortion" that supports outpatient management of medical abortion and reinforces evidence from WHO 2012 and 2015 guidance. (1)
4. Mifepristone-misoprostol combi-packs allow for improved quality assurance of the medications, misoprostol in particular (12), and could facilitate ease of use given that the product has simple instructions for drug administration. (13)
5. The inclusion of the phrase "where permitted under national law and where culturally acceptable" is unnecessary. It is also inconsistent with other WHO Guidelines where no such remarks exist. (14)
    - The inclusion of this phrase creates confusion in the field; often leading to additional and inappropriate restrictions in availability. The box is inconsistent with the standard that medications deemed as essential on the EML are to be legal, safe and effective.

2. Relevant WHO technical department and focal point

WHO Technical Department:
Department of Reproductive Health and Research (RHR), Human Reproduction Programme (HRP) Maternal & Perinatal Health & Preventing Unsafe Abortion (MPA)
UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction

Focal Point (s): Dr. Roopan Gill; Dr. Bela Ganatra

The technical guidance of Ms. Jennifer Blum and the EML secretariat on this application is acknowledged.

3. Name of organization(s) consulted and/or supporting the application

N/A

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine

Table 2. INN and ATC for Mifepristone and Misoprostol

Name	**ATC Code**	**INN**
Mifepristone	G03XB01	5752
Misoprostol	G02AD06	

5. Dose form(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/ strengths (if appropriate)

The dose form(s) and strength(s) of mifepristone 200 milligram tablet and misoprostol 200 microgram oral tablet do not require any specific changes from previous applications.

For the combi-pack the dose form(s) and strength(s) are: mifepristone 200 milligram tablet [1] and misoprostol 200 microgram tablet [4].

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class

The listing is requested as an individual medicine.

7. Treatment details (requirements for diagnosis, treatment and monitoring)

7.1 Dosage regimen

The forthcoming *WHO Guideline: Medical Management of Abortion (1)* recommends a dosage regimen for medical management of induced abortion with a uterine size less than 12 weeks as: **a single dose of 200 milligrams of oral mifepristone** followed by **misoprostol 800 micrograms by either sublingual, vaginal or buccal route** to be administered 1-2 days after mifepristone. The WHO recommendation for route of administration emphasizes consideration of the pregnant person and provider preferences. (1-3, 5)

7.2 Course and duration of treatment

The medical abortion process involves one outpatient visit and possibly two if needed and/or requested by the pregnant person. The entire process occurs over several days; with confirmation of abortion status typically done one to two weeks following administration of mifepristone. Eligible persons should have a pregnancy with uterine size measuring less than 12 gestational weeks, which can be assessed by the last menstrual period, a bimanual pelvic exam or an ultrasound scan. Pregnant persons receive one tablet mifepristone to swallow, which can be taken at home without direct medical supervision. The person is then advised to take 4 tablets of misoprostol 1 to 2 days later. Nine out of ten pregnant people will expel the products of conception in the 4 – 6 hours following administration of misoprostol.(2) Pregnant persons should be counselled that the effects of the medical abortion are similar to those associated with spontaneous abortion (synonymous with miscarriage) and include cramping and prolonged menstrual-like bleeding. Bleeding occurs for 9 days on average but can last up to 45 days in rare cases. (2) Since 2012, WHO Guidance has indicated that routine follow-up is not medically necessary given the high effectiveness of mifepristone-misoprostol for medical abortion. (2)

Support for less medicalized service delivery exists in a number of WHO Guidelines, clinical guidance and systematic reviews. (1-3, 5, 7, 15-17) Specifically, the WHO 2015 *Health worker roles in providing safe abortion care and post-abortion contraception (3)* and the forthcoming, WHO 2018 *Medical Management of Abortion Guidance (1)*, state that administration of mifepristone-misoprostol does not require direct medical supervision or specialized care. The WHO recommends that pregnant persons should be provided information and access to healthcare providers if they are experiencing signs of ongoing pregnancy or for any other medical reasons. (1-3, 5, 18) One health worker can provide the entire package, but it is equally possible for subtasks to be performed by different health workers and at different locations. Table 3 highlights the subtasks and the associated descriptions according to the WHO 2015 guidance.(3) Definitions of the various cadre of health workers and level of evidence for each sub-task is provided in Appendix 1.

Table 3. Medical abortion < 12 weeks subtasks

Subtasks	**Description**
Assessing Eligibility for Medical Abortion	Diagnosing and dating the pregnancy, ruling out medical contraindications, screening for possible ectopic pregnancy
Administering the Medications	Pregnant persons provided tablets for mifepristone and misoprostol which can be self-administered in facility or at home. Instructions on appropriate use and managing common side-effects provided.
Assessment for Completion	Assessing that abortion process is complete and that no further intervention is required

7.3 Need for special diagnostic or treatment facilities and skills

Specialized diagnostics or treatment is not needed. (2) Provision of care generally requires access to quality mifepristone and misoprostol in the correct dosages, instructions on how to use them (including dating of gestational age) and information about how recognize complications (e.g. in the event of very heavy and/or prolonged bleeding) and where to seek help. Ultrasound scanning is not routinely required, (1-3, 5) and routine use of antibiotics and testing for sexually transmitted infections is not recommended. (2, 3, 5) In the event of undiagnosed ectopic pregnancy, heavy, ongoing bleeding and/or retained products of conception that may not evacuate on its own, the pregnant person may require referral to a higher level care. (2, 3, 5)

Evidence supports safe and effective provision of medical abortion for pregnancies less than 12 weeks uterine size by the following health care cadres: auxiliary nurses, auxiliary nurse midwives, nurses, midwives, associate and advanced associate clinicians, non-specialist and specialist doctors. (1-3, 5, 7, 9, 19-22) It is recommended that every primary care health-service delivery point have staff (regardless of their cadre) trained and competent to take a medical history, perform a bimanual and abdominal examination and establish a referral network with higher level facilities and/or providers who are available to manage complicates in the rare event that they may arise.

7.4 Published WHO Guidelines

WHO Safe Abortion: Technical and Policy guidance. This guideline was first issued in 2003 and later in 2012 and provides recommendations for clinical care, while also addressing policy, programmatic and health systems considerations in the provision of safe abortion. Specific thematic areas related to medical abortion regimens in the 2012 Safe Abortion guidance have been updated in the forthcoming WHO Recommendations for Medical Management of Abortion guideline which will be published by the end of 2018.

WHO Clinical Practice Handbook for Safe Abortion. This handbook was issued in 2014. It provides guidance to providers with requisite skills and training necessary to provide safe abortion and/or treat complications of unsafe abortion. It is a practical guide of clinical recommendations from the second edition of *Safe abortion: technical and policy guidance for health systems* (WHO 2012).

WHO Health Worker Roles in providing safe abortion and post-abortion contraception. The guideline was issued in 2015. This guideline contains recommendations on the roles of various health workers in the provision of abortion care, as well as self-management of medical abortion. Please refer to Appendices 1 and 3 for data from these guidelines.

WHO Recommendations on Medical Management of Abortion (Forthcoming). This guideline was approved by the Guideline Review Committee (GRC) at the WHO on October 8, 2018. The expected date of publication is December 2018. This guideline includes recommendations on

medical abortion regimens for management of induced abortion, intrauterine fetal demise and management of incomplete abortion. It also includes an evidence update on use of contraception following medical abortion.

8. Information supporting the public health relevance

8.1 Disease Burden

Despite the major advances in management of abortion over the last two decades, of the 55.7 million abortions that occurred worldwide each year between 2010 -2014, 30.6 million (54.9%,) were considered safe, 17.1 million (30.7%) are classified as less safe and 8.0 million (14.4%) were considered least safe according to new safety classifications. 24.3 million (97%) of unsafe abortions occur in developing countries.(23)

The conceptualisation of abortion safety as safe, less safe and least safe was developed using a theoretical framework that drew from the WHO definition of unsafe abortion and the WHO safe abortion guidelines. (23) Safe abortions are defined as those that are provided by health care workers and done in accordance with WHO guidance. Less-safe abortions include those performed by trained providers using non-recommended methods or using a safe method (e.g. misoprostol only) but without adequate information or support from a trained individual and least safe abortions are defined as those done by untrained persons using dangerous, invasive methods.

Given the need to improve access to safe abortion, the WHO has emphasized the need to address the dearth of trained providers. It the WHO *2015 Health Worker roles in providing safe abortion care and post abortion contraception (3)* guideline, the global deficit of skilled healthcare professionals (midwives, nurses and physicians) in regions where the burden of unsafe abortion is the highest is highlighted (Appendix 2). The guidance provides evidence-based recommendations for a range of health care cadres to have a role in the provision of safe abortion care, thereby helping to address the global deficit of skilled healthcare providers. (3, 6)

8.2 Current Use

According to the Guttmacher Institute, as of 2010-2014, an estimated 36 abortions per 1000 women aged 15-44 occur per year in developing regions, compared to 27 in developed regions. (24). While the total number of medical abortions globally is difficult to estimate, some data are available. For example, a paper from 2017 reported that more 3 million mifepristone-misoprostol medical abortions since the approval of Mifeprex® in the United States. (11) More recently, a study by the Guttmacher Institute estimated 12.7 million medical abortions occur annually in India. (25)

8.3 Target Population

The target population are pregnant persons seeking medical abortion.

8.4 Likely impact of treatment

The impact of treatment on disease has not changed from the original application in 2005. For instance, mifepristone-misoprostol remains the preferred "gold standard" for medical abortion. Regimens using these two medications are associated with a very low rate of ongoing pregnancy, a shortened induction-abortion interval and lower side effect profile compared to medical abortion using misoprostol alone. The existence of a number of WHO evidence-based guidelines as well as hundreds of randomized controlled trials, clinical and non-clinical trials, stand testament to the safely and effectiveness of mifepristone-misoprostol for medical abortion. Improving access to these medications has been shown to impact rates of unsafe abortion and, ultimately, maternal mortality and morbidity have declined. (18, 26, 27)

9. Review of benefits: summary evidence of comparative effectiveness

Evidence for the clinical effectiveness and safety of mifepristone-misoprostol was evaluated at the time of its original listing in 2005. The comparative effectiveness of expectant, medical and surgical effectiveness is largely unchanged. Refined regimens of medical abortion using mifepristone-misoprostol have been shown to result in fewer ongoing pregnancies as compared to the earlier studies, making use of the method more similar to effectiveness of standard surgical management with vacuum aspiration. Treatment failure may occur in 2 – 5% of cases. (2, 15) The WHO recommends that persons with an ongoing pregnancy should be offered either repeat administration of misoprostol or vacuum aspiration. (1, 2, 5)

WHO guidelines and various national and international guidance and systematic reviews have further emphasized that mifepristone-misoprostol medical abortion is safe and effective. (13, 8, 11, 12, 20, 27) In addition, there is evidence of safe and effective use in outpatient and primary health care settings with a wide cadre of health workers without need for direct medical supervision. (1-3, 18, 28-34) The recommendations as they pertain to medical abortion and the respective subtasks that are found in the WHO 2015 guidance are provided in Appendix 3.

Of note, in the forthcoming publication of the ***WHO Recommendations for Medical Management of Abortion***, two systematic reviews were done that further support the effectiveness and safety of mifepristone-misoprostol for medical abortion. Tables presenting the relevant data from papers reviewed are listed in Appendix 4. One of these systematic reviews assessed the safety, efficacy and acceptability of medical abortion at gestational ages between 63 ≤ 84 days.(16) The review includes nine studies that compared medical abortion to surgical abortion, mifepristone-misoprostol versus misoprostol alone (including the different dosages, routes and frequency of dosing of misoprostol) and location of the medical abortion. Effectiveness of medical abortion compared to surgical in the first trimester was found to be 94.6% versus 97.9%. Success rates for all of the abortion regimens were as high as 94.6%. This new review provided further evidence to support the WHO's 2012 recommendations for mifepristone-misoprostol medical abortion. It also formed the scientific rationale for the WHO

to recommend several refinements in terms of the recommended regimen for mifepristone-misoprostol medical abortions in gestations between 63 ≤ 84 days; specifically to include the option of buccal administration of misoprostol and to support a mifepristone-misoprostol dosing regimen that is uniform for all pregnant persons desiring a medical abortion with uterine size less than 12 weeks. (2, 16)

A second systematic review assessed the effectiveness of a mifepristone-misoprostol or misoprostol alone for medical abortions ≤ 63 days gestational age (18). This review is an update of a previous systematic review published in 2011. (8) Forty-one studies were included to compare different routes of misoprostol after administration of mifepristone, different doses of misoprostol in misoprostol-only regimens and to compare management of induced abortion in a healthcare facility and those self-managed by women. Effectiveness of the mifepristone-misoprostol regimen ≤ 63 days was 98% which is consistent with previous reviews. (2, 7, 18)

In terms of mifepristone-misoprostol combi-packs, the benefit is largely to ensure that quality-assured products with consistent dosing and clear instructions are available. Although it did not specifically compare combi-pack to individually packaged mifepristone-misoprostol, one study supported by the WHO in Kyrgyzstan did train midwives and family nurses to provide medical abortion with mifepristone–misoprostol combi-packs. (35) The experience led the authors to recommend registration and market availability of medical abortion combi-packs as a strategy to facilitate the scale up of safe abortion in the country.

The WHO is currently leading an initiative focused on increasing access to quality assured combi-packs that was highlighted during a technical consultation in early 2018. (36). In addition, two global resources now track laws, policies and registrations of medical abortion commodities (https://srhr.org/abortion-policies) and availability of medical abortion commodities (www.medab.org). (37, 38) Both databases are updated regularly to reflect changes as necessary.

10. Review of harms and toxicity: summary of evidence of safety

10.1 Estimate of total patient exposure to date

More than 1000 studies have been published over the last thirty years on the use of mifepristone-misoprostol or misoprostol only in obstetrics and gynecology; with hundreds of thousands of patients exposed to the medications. Since 1988, when mifepristone was first licensed for use for early abortion in France, millions of persons have safely and effectively used mifepristone and misoprostol to terminate a pregnancy. (39) Misoprostol was first patented in 1974 and registered under the name Cytotec for the prevention of gastric ulcers associated with non-steroidal anti-inflammatory drugs. It has also been used extensively since this time for its gastric ulcer indication as well as a range of reproductive health indications. As mentioned above in section 8.2, it is difficult to estimate the total number of mifepristone-misoprostol medical abortions globally, although some data are available. For example, a paper from 2017 reported that more than 3 million people have had a mifepristone medical abortion since the

approval of Mifeprex® in the United States. (11) More recently, a study by the Guttmacher Institute estimated 12.7 million medical abortions occur annually in India. (25)

10.2 Description of the adverse effects/ reactions and estimates of their frequency

Evidence for the clinical effectiveness and safety of mifepristone-misoprostol was evaluated at the time of its original listing in 2005. Data recently published on safety from the United States since mifepristone's approval 16 years ago, found an estimated mifepristone-associated mortality rate of 0.00063%. (10, 11) Studies including mifepristone-misoprostol medical abortions among more than 423,000 persons globally reported very low rates (0.01 to 0.7%) of non-fatal serious adverse events such as hospital admission, blood transfusion or serious infection after use of mifepristone. (11) In addition, a pooled analysis of serious adverse reactions including data from 30,966 clinical study participants presenting for mifepristone-misoprostol medical abortion through 70 days gestation found no differences in rate or type of serious adverse reaction by geographical location. (10) Serious adverse reaction rates were reported in <0.5% of study participants and include atypical presentation of infection, sepsis and prolonged heavy bleeding/hemorrhage, as shown in table 4 below. (10) These events are most always treatable without permanent sequelae.

Table 4. Serious Adverse Reactions Reported in US Mifeprex label among Women Following Administration of Mifepristone (oral) and Misoprostol (buccal) in U.S. and Non-US Clinical Studies. (10)

Adverse reaction	**US**			**Non-US**		
	# of studies	Number of Evaluable Women	Range of frequency (%) #	# of studies	Number of Evaluable Women	Range of frequency (%) #
Transfusion	4	17,774	0.03-0.5%	3	12,134	0-0.1%
Sepsis	1	629	0.2%	1	11,155	<0.01%*
ER visit	2	1,043	2.9-4.6%	1	95	0
Hospitalization Related to Medical Abortion	3	14,339	0.04-0.6%	3	1,286	0-0.7%
Infection without sepsis	1	216	0	1	11,155	0.2%
Hemorrhage	NR	NR	NR	1	11,155	0.1%

*One patient died of sepsis.

Uterine rupture is a rare complication; and usually associated with very high doses of misoprostol only and not the mifepristone-misoprostol medical abortion regimens recommended by WHO. (1, 2) WHO highlights the need for good clinical judgement and health system preparedness for emergency management of uterine rupture in these very rare events.

The most commonly reported adverse reactions (>15%) for mifepristone-misoprostol include: nausea, weakness, fever/chills, vomiting, headache, diarrhea and dizziness. The frequency of adverse reactions varies between studies and depend on many factors including patient population and gestational age. About 85% of users report at least one adverse reaction following administration of mifepristone-misoprostol and many report more than one adverse reaction. Data from three clinical studies totaling 1,248 patients through 70 days gestation who used mifepristone 200 mg orally followed 1-2 days later by misoprostol 800 micrograms buccally reported frequency of nausea, weakness, fever/chills, vomiting, headache, diarrhea and dizziness ranging from 42% to 52% with the least common being diarrhea. (28, 40, 41).

One adverse event that may require hospitalization and blood transfusion is severe vaginal bleeding however studies have found that the overall rate of bleeding varied between 0.5% and 4.2%. (33, 42) Two studies have evaluated clinically significant bleeding by gestational age and concluded that there was no trend of increased bleeding requiring interventions with mifepristone-misoprostol use with increasing gestational age. (33, 42)

Abdominal pain and cramping are expected side effects of medical abortion and its incidence is not systematically reported in clinical studies. Treatment with mifepristone-misoprostol is intended to induce uterine bleeding and cramping and as such, bleeding and cramping are expected consequences of the abortion process. Most persons can expect bleeding more heavily than they do during a heavy menstrual period. (2, 5) The WHO 2012 clinical guidelines and the subsequent 2014 clinical practice guideline state that persons requesting abortion should always be offered medication for pain management (1,2). Pain medications can be offered at the initial visit by various cadres of healthcare providers. (1, 2)

The 2015 WHO recommendations on health worker roles in providing safe abortion care and post-abortion contraception highlight that the most commonly experienced side effects can be managed in primary care and outpatient settings by various cadres of healthcare providers. (3) All persons seeking abortion should be counseled about common side effects after mifepristone-misoprostol medical abortion and told how they can be managed. In deciding on a course of treatment, some pregnant persons may choose regimens with routes of misoprostol that may be associated with higher side effects, but be more consistent with their wishes and expectations of acceptability and overall satisfaction.

10.3 Summary of available data (appraisal of quality, summary of results)

Data from studies that were used for systematic reviews to support the safety and effectiveness of mifepristone-misoprostol for medical abortion are listed in Appendix 4.

10.4 Summary of comparative safety against comparators

This is not applicable to the current application. Safety against comparators was discussed in the WHO Essential Medicines List Application in 2005. The comparators would be expectant management, surgical management and alternative medical methods (i.e. misoprostol alone regimens).

10.5 Identification of variation in safety that may relate to health systems and patient factors

The WHO recommends that abortion care be provided at all levels of care – from primary-care and through outpatient services in higher-level settings as it is safe and minimizes costs while maximizing convenience and timeliness of care. (2, 3, 5) According to this guidance, safe abortion, particularly for pregnant persons less than 12 weeks' by uterine size, can be provided safely on an outpatient basis at the primary care level of the health care system by trained health-care providers, including non-physicians trained in basic clinical procedures related to reproductive health. (2, 3) Current evidence suggests that provision of medical abortion by mid-level providers has no adverse impact on the safety or efficacy of the abortion process. (39) Finally, recommendations for the role of self-management of mifepristone and misoprostol without direct supervision of a health-care provider are made in specific circumstances, in which pregnant persons have the appropriate information and access to health services should they need or want them at any stage of the process. (1-3, 43)

These recommendations take into account the desire to minimize the cost of time away from family to reach an abortion provider, time away from family and work during the abortion process, cost of health system and burden on higher level providers.

Table 5, summarizes use of mifepristone and misoprostol among special populations and overall risk summary drawn largely from drug labels are highlighted below. (10, 44, 45)

Table 5. Risk summaries for special populations

Mifepristone	
Special Population	Risk Summary (10)
Pregnancy	• Risk of adverse developmental outcomes with a continued pregnancy after a failed termination with mifepristone in a regimen with misoprostol is unknown
Lactation	• Present in human milk • Limited information on effects of mifepristone in a breastfed infant or on milk production
Pediatric Use	• Data from clinical study of Mifeprex®(mifepristone), included subset of 322 females under age 17, demonstrating safety and efficacy profile similar to that observed in adults
Misoprostol	
Special Population	Risk Summary (44, 45)
Pregnancy	• Teratogenic effects have been reported subsequent to use of misoprostol, but drug's teratogenic mechanism has not been demonstrated
Lactation	• No published reports of adverse effects of misoprostol in breast-feeding infants of mothers taking misoprostol
Pediatric Use	• Safety and effectiveness in pediatric patients has not been established

11. Summary of available data on comparative cost and cost-effectiveness of the medicine

The price of mifepristone, misoprostol and the combi-packs varies widely by geography. Legal status of abortion, willing marketers and distributors and a perceived sustainable market all impact the cost to the buyer. Market flexibility is being regulated by the increasing number of new products in markets – both individually packaged mifepristone and misoprostol as well as combi-packs. It is the hope of the international community that increasing access to quality MA combi-packs will drive down price while maintaining quality.

In the calculations for this application, data for misoprostol cost are taken from the International Drug Price Indicator Guide (2014). This guide does not currently list mifepristone or mifepristone-misoprostol combi-packs, so the cost for these products has been provided by UNFPA and reflects their supplier cost rate.

Mifepristone

According to the UNFPA catalogue price, the price per 200 mg tablet of mifepristone is ranges from $5.50 - $15.00 (2018). The recommended dose of mifepristone is 1 tablet when used prior to administration of 800 mcg misoprostol (4 tablets). Misoprostol costs are listed below.

Table 6. Cost of Mifepristone

Product	Minimum Price	Maximum Price	Average Price
Mifepristone 200mg tablet (Pack of 1)	$5.50	$15.00	$ 8.52

Note: Special conditions may apply (like minimum/multiple order quantities, etc
Source: UNFPA, 2018, [Personal Communication Dec 4, 2018]
https://www.unfpaprocurement.org/products

Misoprostol

According to the *International Drug Price Indicator Guide* (2014), the median price per 200mcg tablet of misoprostol is 0.3461 US cents, with a range of 0.1717 to 0.5075 US cents. (46) The median price paid by the two buyers listed is USD 0.2269 per tablet (range USD 0.0900-0.3637). The recommended dose of misoprostol when used following mifepristone for medical abortion is 800 mcg, or 4 tablets. Therefore, the median price for misoprostol per person treated would be, 1.38 USD, with a range of 0.6868 US cents to 2.03 USD.

Table 7. Cost of Misoprostol

Misoprostol price information (in US$)			
Supplier Prices			
Source	Package	Package Price	Unit Price
MEDS	30 Tab-cap (Tablets)	5.15	0.1717
MSD/TANZ	20 Tab-cap (Tablets)	6.30	0.3150
MEDEOR/TZ	28 Tab-cap (Tablets)	10.56	0.3771
UNFPA	60, blisters 6 X 10	30.45	0.5075
		Median Price 0.3461/Tab-cap	**High/Low Ratio** 2.96
Buyer Prices			
OECS/PPS	100 Tab-cap (Tablets)	9.00	0.0900
SAFRICA	60 Tab-cap (Tablets)	21.82	0.3677
		Median Price 0.2269/Tab-cap	**High/Low Ratio** 4.04

Source: International Drug Price Indicator Guide (Management Health Sciences, 2014)

In total, when purchased independently the average cost of the medication for a medical abortion (1 tablet mifepristone + 4 tablets misoprostol) ranges from $4.19 to $10.03. When obtained via UNFPA as a combi-pack, the cost ranges from $3.75 to $11.75, as per the table below.

Table 8. Cost of Mifepristone-Misoprostol

Product	Minimum Price	Maximum Price	Average Price
Mifepristone 200mg tablet + 4 misoprostol 200mcg tablets in one blister (Pack of 5)	$3.75	$11.56	$ 6.77

Source: UNFPA, 2018, [Personal Communication : Dec 4, 2018]
https://www.unfpaprocurement.org/products

12. Summary of regulatory status and market availability of the medicine

Mifepristone, misoprostol and combi-packs are available globally. Since 1988, mifepristone has been registered for medical abortion in nearly 60 other countries worldwide. (37) It is sold under several different brand names around the world. Mifepristone is currently marketed throughout Europe, in North America (the United States, Canada and Mexico), South Asia (Bangladesh and India), South-east Asia (Vietnam, Cambodia) as well as China. Currently, its availability in Latin America is largely restricted to Mexico City, Suriname and Colombia; although additional registrations are underway including in Chile. The drug is also registered in Tunisia, South Africa, Ethiopia, Ghana and Benin; again, with plans for further registrations underway in additional countries throughout Africa. A partial list of mifepristone products and their manufacturers is included in Appendix 5.[2]

Misoprostol was originally approved in the United States, where it was marketed and distributed as Cytotec® by Searle, which then became part of Pharmacia, which, in turn merged with Pfizer. Its most commonly marketed under the brand name Cytotec® and is registered in more than eighty countries across the globe. It is available in many countries for its gastric ulcer and postpartum hemorrhage indications. As mentioned above, misoprostol is

[2] This list was comprised from IPPF's Medical Abortion Commodities Database (accessed 11/2018) which includes information on brands of mifepristone, misoprostol or combi-packs that are registered and available in a country and, for misoprostol and combi-packs, have sufficient evidence of good quality. If a product is not listed for a particular country, it is because either a) the product is misoprostol or a combi-pack and does not have sufficient evidence to indicate it's quality; b) the product is not registered in that country; or c) the product was not identified during data collection which involved visiting a minimum of two locations in each country and collecting information on available brands of misoprostol, mifepristone and combi-packs from up to 20 pharmacies and health facilities. Information was also sourced from social marketing organizations, and distributors and stockists. Data collection has not yet occurred in all countries. As new data becomes available, the database will be updated.

currently on the Core list of essential medicines for the following indications: labor induction, incomplete abortion and miscarriage management, postpartum hemorrhage prevention and postpartum hemorrhage treatment. A partial list of misoprostol products and their manufacturers is included in Appendix 6.

Combi-packs of mifepristone-misoprostol began to appear on the market in the last decade and have been slowly increasing in availability. WHO partnered with the Concept Foundation to facilitate the development of Medabon®, the first quality-assured SRA approved mifepristone-misoprostol combi-pack. WHO and Concept Foundation collaborated in facilitating the registration and further distribution of Medabon. WHO has provided CF with the research dossier for this purpose. WHO and CF continue to have a collaboration agreement to increase the availability and accessibility of reproductive health medicines in the public sector of developing countries. To date, no combi-packs have received WHO pre-qualification; however, as of January 2018, there are three mifepristone products and three misoprostol products that are WHO pre-qualified. (36) These are:

Mifepristone: Linepharma International, Zizhu Pharmaceutical Co Ltd., Exelgyn
Misoprostol: Cipla Ltd., Zizhu Pharmaceutical Co Ltd., and Acme Formulations, India

A list of quality-approved mifepristone-misoprostol combi-packs and their manufacturers is included as Appendix 7. A preliminary review commissioned by WHO, and conducted by the Concept Foundation in August 2017, identified 10 manufacturers producing a total of 15 brands of combi-packs for international distribution and an additional eight manufacturers producing a combi-packs for the India market.

In addition, as mentioned above, the WHO Global Abortions Policies Database (37) provides a listing of countries where mifepristone–misoprostol and misoprostol have country level approval (Tables 14 and 15; Appendix 8).

13. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia)

Misoprostol (standards available in BAN, USAN, rINN)
Mifepristone (standards available in BAN, USAN, rINN)

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Appendix 1. Definitions of health workers according to WHO 2015 guidance, tasks and subtasks for medical abortion considered in the guidance

Table 2. Health worker category descriptions

Broad category	Illustrative description for the purpose of the tasks covered in this guideline	Examples
Specialist doctor	For the purpose of this guideline, specialization refers to postgraduate clinical training and specialization in obstetrics and gynaecology.	Gynaecologist, obstetrician
Non-specialist doctor	For the purpose of this guideline, this refers to a medical doctor who holds a university-level degree in basic medical education with or without further training in general practice or family medicine, but not in obstetrics and gynaecology.	Family doctor, general practitioner, medical doctor
Advanced associate and associate clinician	For the purpose of this guideline, this refers to a professional clinician with basic competencies to diagnose and manage common medical and surgical conditions and also to perform some types of surgery. Training can vary by country, but generally requires 3–4 years post-secondary education in an established higher education institution. The clinician is registered and his or her practice is regulated by a national or subnational regulatory authority.	Assistant medical officer, clinical officer, medical licentiate practitioner, health officer, physician assistant, surgical technician, non-physician clinician, medical assistant, nurse practitioner
Midwife	For the purpose of this guideline, this refers to a person who has been registered by a state midwifery or similar regulatory authority and has been trained in the essential competencies for midwifery practice. Training typically lasts 3 or more years in nursing or midwifery school and leads to a university degree or the equivalent. A registered midwife has the full range of midwifery skills.	Registered midwife, midwife, community midwife, nurse-midwife
Nurse	For the purpose of this guideline, this refers to a person who has been legally authorized (registered) to practice after examination by a state board of nurse examiners or similar regulatory authority. Education includes 3 or more years in nursing school, and leads to a university or postgraduate university degree or the equivalent.	Registered nurse, clinical nurse specialist, licensed nurse, BSc nurse
Auxiliary nurse midwife and auxiliary nurse	For the purpose of this guideline, an auxiliary nurse is someone trained in basic nursing skills but not in nursing decision-making. An auxiliary nurse midwife has basic nursing skills and some midwifery competencies but is not fully qualified as a midwife. The level of training may vary from a few months to 2–3 years. A period of on-the-job training may be included, and sometimes formalized in apprenticeships.	Auxiliary midwife, auxiliary nurse, ANMs, family welfare visitor

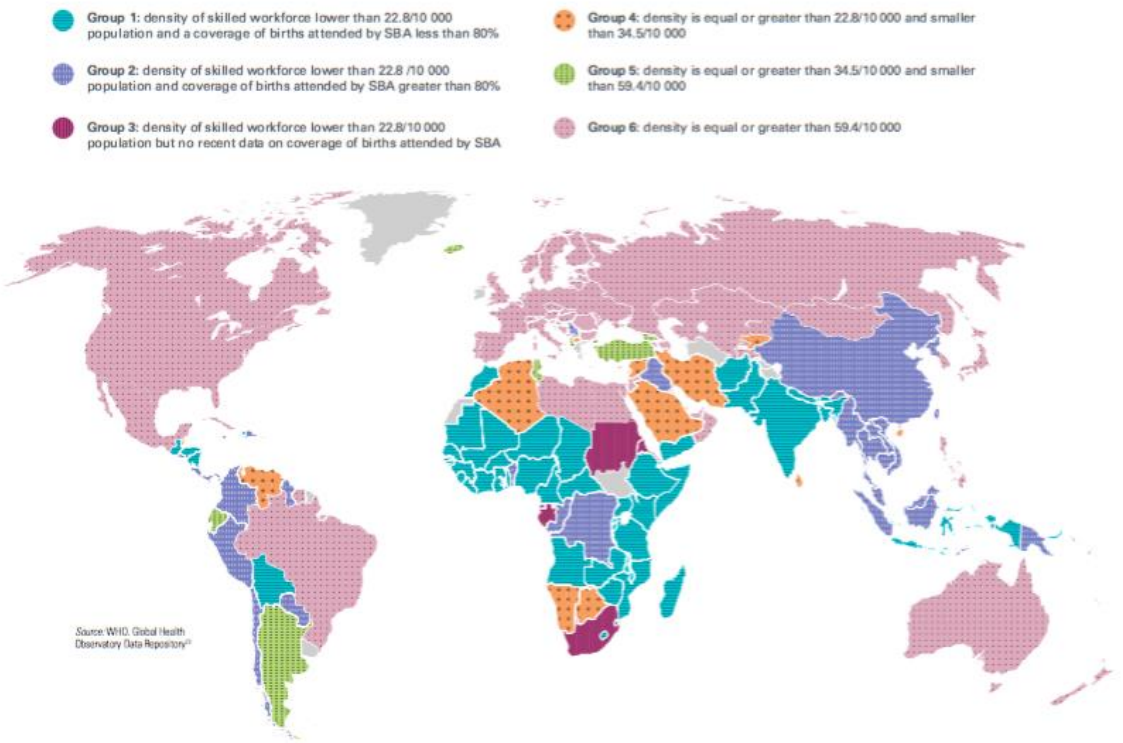
Broad category	Illustrative description for the purpose of the tasks covered in this guideline	Examples
Doctor of complementary systems of medicine	For the purpose of this guideline, this refers to a professional of traditional and complementary systems of medicine (non-allopathic physician) whose training includes a 4- or 5-year university degree that teaches the study of human anatomy, physiology, management of normal labour and the pharmacology of modern medicines used in obstetrics and gynaecology, in addition to their systems of medicine. For the purpose of this guideline, these doctors are included with reference to the provision of elements of abortion-related care as per conventional medical practice.	Ayush doctor, Ayurvedic physician, non-allopathic physician
Pharmacist	For the purpose of this guideline, this refers to a health practitioner who dispenses medicinal products. A pharmacist can counsel on the proper use and adverse effects of drugs and medicines following prescriptions issued by medical doctors/health professionals. Education includes university-level training in theoretical and practical pharmacy, pharmaceutical chemistry or a related field.	Pharmacist (USA), chemist (United Kingdom and the Commonwealth), clinical pharmacist, community pharmacist
Pharmacy worker	For the purpose of this guideline, this refers to technicians and assistants who perform a variety of tasks associated with dispensing medicinal products under the guidance of a pharmacist. They inventory, prepare and store medications and other pharmaceutical compounds and supplies, and may dispense medicines and drugs to clients and instruct on their use as prescribed by health professionals. Technicians typically receive 2–3 years training in a pharmaceutical school, with an award not equivalent to a university degree. Assistants have usually been through 2–3 years of secondary school with a subsequent period of on-the-job training or apprenticeship.	Pharmacy assistant, pharmacy technician dispenser, pharmacist aide, dispensary assistant
Lay health worker	For the purpose of this guideline, this refers to a person who performs functions related to health-care delivery/ information provision and was trained in some way in the context of the task, but has received no formal professional or paraprofessional certificate or tertiary education degree.	Community health worker, village health worker, female community health volunteer

Table 1. Tasks and subtasks considered in the guideline

Specific tasks included in the scope of the guideline
Management of abortion and post-abortion care in the first trimester • Vacuum aspiration for induced abortion • Vacuum aspiration for the management of incomplete abortion • Medical abortion with mifepristone + misoprostol or misoprostol alone, including the subtasks of: – assessment of eligibility – administration of medications and management of the process – assessment of abortion completeness • Medical management of incomplete abortion with misoprostol • Self-management of components of medical abortion
Management of abortion and post-abortion care beyond 12 weeks • Dilatation and evacuation (D&E) for induced abortion, including specific subtasks as follows: – cervical priming with osmotic dilators – cervical priming with medications • Medical abortion with mifepristone + misoprostol or misoprostol alone
Recognizing and managing non-life-threatening complications • Initial management of non-life-threatening post-abortion infection • Initial management of non-life-threatening post-abortion haemorrhage
Counselling and information provision • Provision of general information on safe providers, laws, contraception options • Pre- and post-abortion counselling
Post-abortion contraception provision • Insertion and removal of IUDs • Insertion and removal of implants • Initiation and continuation of injectable contraceptives • Tubal ligation (female sterilization)

Appendix 2. Figure of health workforce to population ratios in 186 countries

Figure 1: Health workforce to population ratios in 186 countries



Source: WHO, 2013 *(2)*; using data from Global Health Observatory Data Repository (online database), available at: http://apps.who.int/gho/data/

Appendix 3: WHO 2015 Health worker guideline recommendations for provision of medical abortion < 12 weeks

Recommendation category	Symbol	Explanation
Recommended		The benefits of implementing this option outweigh the possible harms. This option can be implemented, including at scale.
Recommended in specific circumstances		The benefits of implementing this option outweigh the possible harms in specific circumstances. The specific circumstances are outlined for each recommendation. This option can be implemented under these specific circumstances.
Recommended in the context of rigorous research		There are important uncertainties about this option (related to benefits, harms, acceptability and feasibility) and appropriate, well designed and rigorous research is needed to address these uncertainties.
Recommended against		This option should not be implemented.

Table 5. The provision of medical abortion (MA) in the first trimester*

Health worker	Recommendation	Justification
Specialist doctors, non-specialist doctors	Recommended 	Within their typical scope of practice. No assessment of the evidence was therefore conducted.
Associate and advanced associate clinicians	Recommended 	There is evidence for the effectiveness of carrying out components of the task, e.g. assessing gestation as part of MVA provision. There is also evidence that health worker types with similar or less comprehensive basic training (e.g. midwives, nurses, auxiliary nurse midwives) can provide MA safely and effectively (moderate certainty). The option is feasible and the potential to expand access to underserved populations is high.
Midwives	Recommended 	There is evidence for the safety and effectiveness of this option (moderate certainty). More women are satisfied with the provider when midwives provide MA (moderate certainty). The option appears feasible and is already being implemented in several countries.
Nurses	Recommended 	There is evidence for the safety and effectiveness, and for women's satisfaction with abortion services with this option (moderate certainty).
Auxiliary nurses and auxiliary nurse midwives	Recommended 	There is evidence for the safety and effectiveness (moderate certainty) of this option. The option appears feasible and is already being implemented in some low-resource settings.

Health worker	Recommendation	Justification
Doctors of complementary systems of medicine	Recommended in specific circumstances  We recommend this option only in contexts with established health system mechanisms for the participation of doctors of complementary systems of medicine in other tasks related to maternal and reproductive health.	There is evidence for the safety and effectiveness, and for women's satisfaction with this type of provider and services (low certainty). The benefits outweigh any possible harms, and the potential to reduce inequities in access to safe abortion care in regions where such professionals form a significant proportion of the health workforce is high.
Pharmacists	No recommendation for independent provision of MA; see Table 6 for recommendations made for subtasks.	Before making a recommendation on full independent provision of MA it is necessary to demonstrate the effectiveness and feasibility of the subtasks.
Pharmacy workers	Recommended against 	There was no evidence for the safety, effectiveness, acceptability or feasibility of this option. However, it is important to note that as with all other drugs and medications, pharmacy workers should dispense mifepristone and misoprostol as indicated by prescription.
Lay health workers	No recommendation for the overall package; see Table 7 for recommendations made for subtasks.	Before making a recommendation on full independent provision of MA it is necessary to demonstrate the safety and feasibility of carrying out the subtasks.

* Refer to MA1 and subtasks framework in Web Supplement 1 (p. 25) for summary of evidence.

Table 8. Women's role in managing the process of medical abortion*

Woman's role	Recommendation	Justification
Managing the entire process of medical abortion up to 84 days	No recommendation for the overall package; recommendations made for subtasks as below.	Individual components of the self-management of medical abortion have been tested; however, there is as yet insufficient evidence on using all three components together.
Self-assessing eligibility for medical abortion	Recommended within the context of rigorous research 	Women may be more conservative in assessing eligibility using simple checklists (low certainty). However, the approach is promising and further work is needed on developing appropriate assessment tools.
Managing the mifepristone and misoprostol medication without direct supervision of a health-care provider	Recommended in specific circumstances  We recommend this option in circumstances where women have a source of accurate information and access to a health-care provider should they need or want it at any stage of the process.	There is evidence that the option is safe and effective (low-certainty evidence from numerous studies, but using non-randomized designs given the strong preferences of women for one or the other option). More women report the method to be satisfactory when it is self-managed (low certainty). Women find the option acceptable and feasible (high confidence) and providers also find the option feasible (high confidence).
Self-assessing completeness of the abortion process using pregnancy tests and checklists	Recommended in specific circumstances  We recommend this option in circumstances where both mifepristone and misoprostol are being used and where women have a source of accurate information and access to a health-care provider should they need or want it at any stage of the process.	There is evidence that the option is safe and effective including in low-literacy, low-resource settings (moderate to high certainty).

Management of non-life-threatening complications

	Lay health workers	Pharmacy workers	Pharma-cists	Doctors of comple-mentary systems of medicine	Auxiliary nurses/ ANMs	Nurses	Midwives	Associate/ advanced associate clinicians	Non-specialist doctors	Specialist doctors
Initial management of post-abortion infection	✗**	✗**	✗**	✓	✓	✓	✓	✓	✓*	✓*
Initial management of post-abortion haemorrhage	✗**	✗**	✗**	✓	✓	✓	✓	✓	✓*	✓*

* considered within typical scope of practice; evidence not assessed.
** considered outside of typical scope of practice; evidence not assessed.

Pre- and post-abortion counselling

	Lay health workers	Pharmacy workers	Pharma-cists	Doctors of comple-mentary systems of medicine	Auxiliary nurses/ ANMs	Nurses	Midwives	Associate/ advanced associate clinicians	Non-specialist doctors	Specialist doctors
Pre- and post-abortion counselling	✓	✗	✗	✓	✓	✓	✓	✓	✓*	✓*

Provision of information on safe abortion

	Lay health workers	Pharmacy workers	Pharma-cists	Doctors of comple-mentary systems of medicine	Auxiliary nurses/ ANMs	Nurses	Midwives	Associate/ advanced associate clinicians	Non-specialist doctors	Specialist doctors
Information on safe providers/ laws	✓	✓	✓	✓*	✓*	✓*	✓*	✓*	✓*	✓*

* considered within typical scope of practice; evidence not assessed.

Appendix 4: Summary of studies included in two systematic reviews of MA up to 84 days

Table 9. Summary of studies included in systematic review of MA ≤ 63 days (18)(19)

S.No	Author, year	Methods	Participants	Interventions	Outcomes
1.	Arvidsson et al 2005	RCT. Women were randomised using computerised randomisation into an oral or vaginal group.	Amenorrhea up to 49 days, no existing contraindications for medical abortion and the woman herself wishing a medical abortion	0.4 mg of misoprostol administered orally (N=48) vs. 0.8 mg of misoprostol administered vaginally (N=49)	pain, duration of bleeding, complications, Preference and acceptability
2.	Aubeny et al 2000	RCT. The randomization list was generated through the ALEA function of Microsoft Excel software.	Women with pregnancies of up to 49 days' gestation who had chosen to terminate their pregnancy by medical method	400 mcg of misoprostol administered orally (N=119) vs. 400 mcg of misoprostol administered vaginally (N=118)	Time of expulsion, Tolerability, Patient-perceived preference, Success of the treatment (percentage of women with a complete abortion without the need for any surgical procedure)
3.	Blanchard et al 2005	The randomization scheme was determined in advance at the Population Council in NewYork, using the pseudorandom number generator in SPSS	Women seeking pregnancy termination at 56 days or less of amenorrhea.	400 mcg oral every 3h for 4 doses (n=36) vs. 800 mcg oral every 6h for 2 doses (n=24) vs. 600 mcg vaginal for 1 dose (n=40)	Defined success as complete abortion without any surgical intervention.
4.	Blum et al 2012	Treatment allocation assigned in blocks of 10 using a computer-generated random sequence created by staff at Gynuity Health Projects	Pregnant women presenting for early medical abortion up to 63 days since their last menstrual period	Combined mifepristone–misoprostol (n=220) vs Mifepristone-only (n=221)	The primary outcome measure was complete uterine evacuation without surgical evacuation for any reason.
5.	Chai et al 2013	Randomization assignment was made by the research nurse using a computer program to allocate the study	Healthy women aged 18 years or older who requested termination of pregnancy of up	800 mcg misoprostol administered via buccal route (N=45) vs.	The primary outcome measure was the proportion of women with fever, defined as

S.No	Author, year	Methods	Participants	Interventions	Outcomes
		subjects into two groups	to 63 days' gestation.	800 mcg misoprostol administered via sublingual route (N=45)	temperature >38°C
6.	Chawdhary et al 2009	Randomization into two groups was done by making the first woman pick a labeled envelope containing information to which group she was designated to. The next candidate was subsequently enrolled to the other group (continued on for all other study participants).	TVS demonstrating an intact single IUP up to a 63-day period of gestation	200 mg oral mifepristone on day 1 and vaginal misoprostol 800 ug on day 3; (n=50) vs. vaginal misoprostol (800 ug) on day 1 and 3 (total dose 1600 ug); (n=50)	The primary outcome measure was complete abortion others:ongoing pregnayc, side effects
7.	Chen, 2006	Group assignment was performed in randomized fashion by using sequentially numbered opaque envelopes containing a card with computer-generated assignment information and prepared for each center by the Data Coordinating Center	Women with pregnancies up to 63 days' gestation by ultrasound examination who desired a medication abortion	Misoprostol 800 Ag vaginally 6–8 h after the mifepristone dose.(n=457) vs. Misoprostol 800 Ag vaginally 24 h after the mifepristone dose. (n=460)	Duration and Quantity of bleeding
8.	Chong et al 2012	Allocation was determined based on a random code generated in blocks of 10 by Gynuity Health Projects in New York, whose staff packed the pills and organized them in sequential, sealed envelopes.	Women who presented for termination of pregnancy with gestations up to 63 days since LMP	400-mcg of buccal misoprostol. (n=559) vs. 800-mcg of buccal misoprostol. (n=563)	Success was defined as a complete abortion using mifepristone and misoprostol without any surgical intervention.
9.	Coyaji et al 2007	The groups were created using a randomisation sequence generated by a computer (using a randomised block design, with blocks of ten to ensure equal	Women seeking termination of intrauterine pregnancies could participate if they had amenorrhoea of 8 weeks or less	two doses of 400 microgram oral misoprostol taken in 3 hours interval (n=150) vs. single dose of 400 microgram	The primary study outcome was complete abortion without surgical intervention. Others:ongoing pregnacy, side

S.No	Author, year	Methods	Participants	Interventions	Outcomes
		numbers in each group during the study.		oral misoprostol (n=150)	effects, expulsion time, satisfaction
10.	Creinin et al 2001	Randomization was performed in blocks of ten using a random number table	Age at least 18 years, a singleton intrauterine pregnancy not exceeding 49 days' gestation as documented by vaginal ultrasound, request for an abortion,	misoprostol 800 mcg vaginally (n=40) vs misoprostol 400mcg orally (n=40)	The primary study outcome was complete abortion without surgical intervention. Others:ongoing pregnacy, side effects
11.	Creinin et al 2004	Group assignment was performed in a randomized fashion by using sequentially numbered opaque envelopes containing a card with computer-generated assignment information and prepared for each center by the Data Coordinating Center	Healthy women requesting an elective abortion, had an intrauterine pregnancy less than or equal to 63 days of gestation on the day of mifepristone administration as confirmed by vaginal ultrasound	misoprostol 800 mcg vaginally 6–8 h after the mifepristone (n=540) vs misoprostol 800 mcg vaginally 23-25 h after mifepristone (n=540)	The primary study outcome was complete abortion without surgical intervention. Others:side effects, acceptability data
12.	Creinin et al 2007	Group assignment randomized using sequentially numbered opaque envelopes containing a card with computer generated assignment information and prepared for each center by the Data Coordinating Center.	Healthy women requesting elective abortion, intrauterine pregnancy ≤63 days of gestation on day of mifepristone confirmed by vaginal ultrasound	800 mcg vaginal within 15 minutes of swallowing mifepristone. (n=567) vs 800 mcg vaginal 23–25 hours after taking mifepristone.(n=561)	The primary study outcome was complete abortion without surgical intervention. Others:ongoing pregnacy, side effects, acceptability data
13.	Creinin M. D et al 2001	Randomisation was performed using a random number table. The group was assigned by opening the next sequentially	A singleton IUP not exceeding a gestation age of 49 days as documented by	misoprostol 400 mcg orally six to eight hours after taking the mifepristone.(n=50) vs	The primary study outcome was complete abortion without suction evacuation. Others:ongoing

S.No	Author, year	Methods	Participants	Interventions	Outcomes
		numbered sealed opaque envelope.	vaginal ultrasound requesting an elective abortion	misoprostol 400 mcg orally 48 after taking the mifepristone. (n=50)	pregnacy, side effects
14.	Dahiya et al 2011	Group assignment was done in a randomized fashion by computer generated random tables.	Healthy women with intrauterine pregnancy <56 days	400 mcg of oral misoprostol 24 h after mifepristone .(n=48) vs 400 mcg of sublingual misoprostol 24 h after mifepristone (n=45)	The main outcome interpreted was complete abortion determined by history of passage of products of conception and confirmed by ultrasonography done after 7 days of misoprostol administration. others: ongoing pregnancy, side effects,
15.	Dahiya et al 2012	Group assignment not described	women with amenorrhea <56 days, age >18 years, request for elective abortion with the indication as per the guidelines of the 1971 MTP act,	mifepristone 200 mg was given orally and misoprostol 800 mcg via buccal route after 24 h (four tablets 200 mcg each). (n=50) vs misoprostol 800 mcg via buccal route (four tablets 200 lg each) (n=50)	The main outcome complete abortion without surgical intervention. others: ongoing pregnancy, side effects, acceptability.
16.	el-Refaey et al 1994	Women were randomised using sealed, opaque envelopes to one of two groups.	women requesting termination of pregnancy of less than 56 days amenorrhea	Single dose regimen received misoprostol ORAL 800mcg.(n=75) vs Misoprostol ORAL 400 mcg which was	The main outcome complete abortion others: ongoing pregnancy, side effects, BP changes

S.No	Author, year	Methods	Participants	Interventions	Outcomes
				repeated 2 h later .(n=75)	
17.	El-Refaey et al 1995	A series of numbered, sealed, opaque envelopes contained the computer-generated random assignments.	women requesting termination of pregnancy within 63 days from the onset of amenorrhea	oral misoprostol (800mcg)(n=130) vs vaginal misoprostol (800 mcg) (n=133)	The main outcome: expulsion of the conceptus without the need for a surgical procedure, others: ongoing pregnancy, missed or incomplete abortion, expulsion time, side effects,
18.	Fekih et al 2010	The assigned treatment group was written on a card and sealed in opaque envelopes that were consecutively numbered and opened immediately before the first drug dose was administered.	Women requesting termination of pregnancy of less than or equal to 56 days from their LMP	200 mg of oral mifepristone followed by 400 µg of oral misoprostol (n=126) vs 800 µg of sublingual misoprostol repeated every 4 hours for up to a maximum of 3 doses (n=126)	The primary outcome measure was the mean drop in hematocrit. Others: ongoing pregnancy, duration of bleeding, recourse to uterotonics, expulsion time, satisfaction and side effects
19.	Garg et al 2015	Patients were divided into two groups and each patient was assorted to one of the groups by random number tables.	age 18 years and above requesting for an elective termination of pregnancy well within the MTP Act. and intrauterine pregnancy of less than or equal to 49 days	800 mcg of misoprostol via buccal route 48 hr after mifepristone (n=25) vs 800 mcg of misoprostol vaginally 48 hr after mifepristone (n=25)	The main outcome complete abortion without surgical intervention others:side effects,

S.No	Author, year	Methods	Participants	Interventions	Outcomes
20.	Goel et al 2011	Women were randomized in blocks of eight using a random number table to create two groups of 40 subjects each. Women were asked to open the next sequentially numbered sealed envelope and assigned to a group accordingly.	healthy pregnant women, who were requesting an elective abortion and had a single intrauterine pregnancy of <7 weeks (49 days) of gestation,	200 mg mifepristone orally and insert 400 mcg misoprostol vaginally simultaneously (n=40) vs insert the misoprostol tablets 24 h after taking mifepristone orally. (n=40)	The primary outcome measure was to compare the complete abortion rates in the two groups. Secondary outcomes included the induction–abortion interval, ongoing pregnancy, adverse effects and acceptability rates.
21.	Guest et al 2007	The randomisation code for assignment to control or study groups was computer generated in fixed blocks of 20 in a 1:1 ratio and concealed in a sealed, opaque envelope.	An IUP confirmed on pelvic ultrasound scan, gestation not exceeding 63 days at the administration of mifepristone and participants must be aged 16 years or older, seeking a termination of pregnancy,	misoprostol 800 micrograms vaginally after 6 hours of mifepristone (n=225) vs misoprostol 800 micrograms vaginally after 36–48 hours of mifepristone (n=225)	primary outcome measure was successful termination rate. Others: ongoing pregnancy, duration of bleeding, satisfaction and side effects
22.	Hamoda et al 2005	Women wishing to participate gave written consent and were randomised to sublingual or vaginal administration by opening sealed opaque envelopes generated using random number tables.	Women with a viable singleton IUP (confirmed by transvaginal ultrasound scan) requesting medical abortion up to 13 weeks of gestation were asked to participate.	misoprostol 600 mcg, given sublingually followed 3 hours later by a further dose of misoprostol 400 mcg, administered sublingually (n=57) vs misoprostol 800 mcg given vaginally, followed 3 hours later by a further dose of misoprostol 400 mcg, administered vaginally (n=72)	Main outcome measures Women's acceptability, efficacy of the regimen and side effects experienced, expulsion time.

S.No	Author, year	Methods	Participants	Interventions	Outcomes
23.	Jain et al 2002	Randomization was based on a computer-gnerated randome nmber table	A totla of 250 healthy women desiring termination of pregnancies < 56 days gestation were enrolled	200 mg of oral mifepristone followed by 800 µg of vaginal misoprostol (n=125) vs 800 µg of vaginal misoprostol repeated every 24 hours; maximum of 3 doses (n=125)	primary outcome measure was successful abortion rate. Others: ongoing pregnancy, duration of bleeding, and side effects
24.	Middleton et al 2005	After the woman swallowed mifepristone 200 mg, a sealed envelope containing the computer-generated random misoprostol route of administration assignment was opened. Women were randomized in blocks of 8 using a scheme created by study staff.	women seeking abortion with pregnancies through 56 days LMP	800 mcg of misoprostol via buccal route 1-2 days after mifepristone (n=223) vs 800 mcg of misoprostol via vaginal route 1-2 days after mifepristone (n=219)	The main outcome was defined as a complete abortion without surgical intervention at any time. Others:ongoing pregnacy, side effects, satisfaction
25.	Ngoc et al 2011	Treatment group was assigned by a computer-generated random sequence in blocks of 10 created at Gynuity Health Projects in New York	Women with GA up to 63 days by LMP, living and working within an hour from the hosptial desiring medical abortion	miso alone --> placebo + 800mcg buccal miso 24 hrs later + 800mcg buccal miso at 48 hrs vs mife + miso combined --> mifepristone 200mcg+ 800mcg buccal miso 24 hrs later + placebo 24 hrs after miso	The primary outcome measure was complete uterine evacuation without recourse to surgical intervention for any reason. Othes:side effect, satisfaction
26.	Okman Kilic et al 2004	Randomization method not mentioned.	> 18 years of age, good health, IUP< 12 weeks'	800 mcg misoprostol (in the form of four 200 mcg tablets	complete uterine evacuation using the medical regimen without

S.No	Author, year	Methods	Participants	Interventions	Outcomes
			gestational age confirmed by ultrasound	after moistening with three drops of water per tablet) by the rectal route (n=30) vs 800 mcg misoprostol (in the form of four 200 mcg tablets after moistening with three drops of water per tablet) by the vaginal route (n=30)	the need for surgical intervention
27.	Prasad et al 2009	Women with even serial numbers were assigned for medical termination, designated as group I. Those with odd serial numbers were allocated to undergo surgical evacuation, designated as group II.	Women with GA up to 49 days desiring abortion	medical abortion misoprostol 800mcg per vagina (single dose; saline-soaked) vs surgical intervention	Efficacy, side effects, complications, and acceptability were assessed in both groups
28.	Raghavan et al 2009	Allocation to oral or sublingual route was determined based on a random code generated in blocks of 10 and printed on slips by Gynuity Health Projects in New York, and organized in sequential, sealed envelopes.	Women with GA through 63 days by LMP presenting for TOP	SL miso mifepristone 200mg + miso 400mcg SL 24 hrs later vs PO miso mife 200mg + miso 400mcg PO 24 hrs later	The primary outcome of the study was to evaluate whether the sublingual route was more efficacious than 400- mcg oral misoprostol through 63 days gestation. Secondary outcomes included assessing the frequency and duration of side effects, acceptability of side effects, and overall satisfaction with the method.

S.No	Author, year	Methods	Participants	Interventions	Outcomes
29.	Raghavan et al 2010	Providers instructed women on the route of misoprostol administration by opening sealed envelopes in sequential order indicating assignment of route. The envelopes were prepared by Gynuity Health Projects staff in New York based on a computer-generated random code.	Women with GA through 63 days by LMP presenting for TOP	Buccal miso mifepristone 200mg + miso 400mcg buccal 24 hrs later vs SL miso mife 200mg + miso 400mcg SL 24 hrs later	Efficacy through 63 days' LMP was the primary outcome Secondary outcomes included the proportion of women experiencing adverse effects and the satisfaction and acceptability of the procedure to women.
30.	Schaff et al 2000	Women drew their concealed computer generated randomized assignments of misoprostol 1, 2 or 3 days after mifepristone.	Women no more than 63 days pregnant, confirmed by sonogram, desiring an abortion	3 arms: miso interval after mife, 1 day, 2 days, 3 days 1) mifepristone 200mg + miso 800mcg PV 1 day later vs 2) mifepristone 200mg + miso 800mcg PV 2 days laters vs 3) mife 200mg + miso 800mcg PV 3 days later	main outcome-effectivness (complete medical abortion without surgical intervention) others: adverse effects. Acceptability, ongoing pregnancy.
31.	Schaff et al 2001	On Day 1, after informed consent, women drew their computer-generated randomized assignments of either misoprostol orally or vaginally at 1 day after mifepristone (at least 24 h after mifepristone up to midnight of Day 2).	Women no more than 63 days pregnant, confirmed by sonogram, desiring an abortion	Mife+miso PO Mifepristone 200mg+ miso 800mcg PO 24 hrs later (400mcg, then another 400mcg miso 2 hours later, last dose no later than midnight on day 2) n=548 Vs mife+miso PV Mife 200mg+ miso 800mcg PV 24 hours later N=596	The primary outcome measures were a complete medical abortion by the first or by the second follow-up visits others: ongoing pregnancy, side effects, satisfaction

S.No	Author, year	Methods	Participants	Interventions	Outcomes
32.	Schaff et al 2002	Randomization was computer generated by each site.	Women no more than 63 days pregnant, confirmed by sonogram, desiring an abortion	1) Mife+miso PO Mifepristone 200mg+ miso 400mcg PO 48 hrs later n=220 Vs 2) Mife+miso 800 PO Mife 200mg+ miso 800mcg PO 48 hours later N=269 vs 3) Mife_miso PV Mife 200mg + miso 800mcg PV 48 hrs later N=522	The primary outcome measures were a complete medical abortion by the first or by the second follow-up visits others: ongoing pregnancy, side effects, satisfaction
33.	Shannon et al 2006	Group assignment, allocated according to a computer-generated random number of blocks of 15. Randomisation was concealed from providers and participants	Women with GA less than 57 days desiring elective abortion	3 arms by miso route 1) mife 200mg + miso 400mcg PO 24-48 hrs later at home vs 2) mife 200mg + miso 600mcg PO 24-48 hrs later at home vs mife 200mg+ miso 800mcg PV 24-48 hrs later	Main outcome measures Successful abortion without surgery. others:ongoing pregnancy, side effects, satisfaction
34.	Tang et al 2003	The women were randomized according to computer-generated random numbers into two groups, vaginal and sublingual.	Women with gestational age </= 9 weeks, confirmed by US, desiring TOP	Mife+miso SL Mife 200mg+ miso 800mcg SL 48 hrs later N=112 vs Mife + miso PV Mife 200mg+ miso 800mcg PV 48 hrs later N=112	The primary outcome measure was the complete abortion rate. Others: ongoing pregnancy, the haemoglobin level, duration of vaginal bleeding and side-effects of treatment
35.	Tendler et al 2015	Randomization was achieved by random withdrawal of an envelope out of 100 pre-assigned envelopes for either regimen.	Women no more than 55 days gestaional age desiring medical abortion	Mife+miso 2 hours later Mife 600mg + 400mcg miso PO 2 hrs later vs Mife+ miso 48 hrs later Mife 600mg + 400mcg miso PO 48 hrs later	Main outcome measure- Procedure failure others:ongoing pregnancy, side effects

S.No	Author, year	Methods	Participants	Interventions	Outcomes
36.	Verma et al 2011	Sequential randomization was done using allocation ratio of 1:1.	Women less than 63 days choosing medical abortion	Mife+ miso interval of 24 hrs Mife 200mg + miso 400mcg PV after 24 hours N=100 vs Mife + miso interval of 48 hours Mife 200mg+miso 400mcg PV after 48 hrs N=100	The primary outcome measure was complete expulsion and induction abortion interval. Secondary outcomes included side effects and tolerability of the two treatment regimens.
37.	Verma et al 2017	The subjects recruited in the study were randomized in two groups using computer software.	Women up to 63 days choosing medical abortion	Mife+ miso simultaneous admin (interval comparison) Mife 200mg + miso 400mcg PV concurrently N=100 vs Mife + miso interval of 48 hours Mife 200mg+miso 400mcg PV after 48 hrs N=100	The primary outcome was to compare the rates of complete abortion in two groups. Secondary outcomes were to compare induction abortion interval, side effects and compliance.
38.	von Hertzen et al 2007	Used a computer generated randomisation sequence to assign 192 participants within every centre	Women with single IUP </= 63 days verified by US, requresting termination of pregnancy	4 arms with comparison to route and interval dosing 1: miso 800mcg SL every 3 hrs x 3 doses vs 2: miso 800mcg SL every 12 hours x 3 doses vs 3: miso 800mcg PV every 3 hrs x 3 doses vs 4: miso 800mcg PV every 12 hrs x 3 doses	The primary outcome measure was efficacy of the treatment in inducing abortion Others: ongoing pregnancy, side effects, expulsion time

S.No	Author, year	Methods	Participants	Interventions	Outcomes
39.	von Hertzen et al 2009	A computer-generated randomisation sequence was produced by WHO staff in Geneva to assign participants within each centre to one of the four dose-interval combinations	women with IUP with duration </=63 day verified by ultrasound, requesting termination of pregnancy	4 arms with comparison to mife dosage and interval between mife-miso 1: mife 100mg+ miso 800mcg PV 24 hrs later vs 2: mife 100mg + miso 800mcg PV 48 hrs later vs 3: mife 200mg+ miso 800mcg PV 24 hrs later vs 4: mife 200mg + miso 800mcg PV 48 hrs later	main outcome was complete abortion. Others: adverse effects, ongoing pregnancy, expulsion time, womens' perceptions of the treatments.
40.	von Hertzen et al 2010	At each of the participating centres, eligible women were allocated randomly to the four treatment groups using a computer-generated randomisation sequence in blocks of variable size.	women with IUP with duration </=63 day verified by ultrasound, requesting termination of pregnancy	4 arms with comparison to miso dosage and route 1: mife 200mg+ miso 400mcg SL 24 hrs later vs 2: mife 200mg + miso 800mcg SL 24 later vs 3: mife 200mg+ miso 400mcg PV 24 hrs later vs 4: mife 200mg + miso 800mcg PV 24 hrs later	The primary outcome was the efficacy of the treatment in achieving complete abortion. Secondary outcomes included the proportion of continuing live pregnancies, the induction-to-abortion interval, adverse effects and women's perceptions about the treatment.
41.	Winikoff et al 2008	Group allocation determined by computer-generated assignment concealed in sealed opaque envelopes. Randomization sequence (using random blocks of 8 and stratified by study center) and envelopes prepared by Gynuity Health Projects staff unrelated to the clinical study conduct	women with pregnancies through 63 days since the LMP.	Mife+ miso oral mife 200mg + miso 800mcg PO 24-36 hours later at home vs Mife+ miso buccal mife 200mg + miso 800mcg buccal 24-36 hours later at home	The primary outcome-treatment success. Secondary outcome variables were the effect of a second dose of misoprostol, adverse effects, patient satisfaction and acceptability of each of the regimens, adverse effects, and pain

Table 10. Aspiration versus medical abortion

Study	Design	Inclusion criteria	Regimen/ comparison	Results	Limitations
Ashok [1], 2002 Scotland Single site	Partial RCT medical versus surgical	Healthy, seeking abortion and eligible for either medical abortion (MA) or vacuum aspiration (VA) - singleton - confirmed by US Those willing to be randomized were GA 10-13 weeks	Vacuum aspiration under general anesthesia (cervical priming with misoprostol 800 mcg 3h prior) Mifepristone 200mg, 36-48h later 800 mcg PV misoprostol (400 mcg q3 up to 2 doses)	**Efficacy** (VA vs MA): Complete abortion 237/242 vs. 192/203 Failed abortion 5/242 vs 11/203 pregnancy 0/242 Median MA interval 5h; median doses miso 2 5 hours (range 2.00-27.58); dose 2 (range 0-3) **Side effects** (denominator those who had SE) (VA vs MA): Nausea 50/180 vs 128/186 Vomiting 15/180 vs 91/186 Diarrhea 8/180 vs 79/186 **Safety** (up to 8 weeks after) (VA vs MA): Heavy bleeding 2/242 vs 4/203 Transfusion 1/242 vs 0/203 Presumed pelvic infection 17/207 vs 7/158 **Acceptability** ('preference' of VA vs MA):	Partially randomized (those who chose their group appeared similar to randomized in terms of GA, age, etc.) Misoprostol use for cervical priming prior to aspiration (may confound side effects)

				Would have same method in future 76/96 vs 47/67	
Robson, 2009 [2] UK Single site	RCT (combined data with non-randomised prospective cases)	Healthy women able to consent >16 yo seeking abortion GA <14 wks	Vacuum aspiration (6<14 wks) Mifepristone 200 mg, 36-48h later 800mcg PV miso (q 3 h 400 mcg) up to 4 doses	**Side effects** (randomized VA vs MA): Nausea 3.3% vs 20.9% (n not provided) Vomiting 2.6% vs 0.8% (n not provided) Diarrhea 0.6% vs 5.3 % (n not provided) **Safety** (randomized VA vs MA): Hospitalization 0/187 vs 4/162 Suspected infection 11 cases (unknown groups) Transfusion 4 cases (unknown groups) Failed VA/MA resulting in uterine perforation/laparotomy n=1 **Acceptability** ('would you opt for the same method' (randomized VA vs MA): (2 wks after abortion): 94% (n=134) vs. 69% (123) Difference between method (VA vs MA) acceptability increases with GA	Data not disaggregated by GA Data (%) presented without denominators/ sample

Table 11. Combined mifepristone/ misoprostol versus misoprostol alone

Study	Design	Inclusion criteria	Regimen/ comparison	Results	Limitations
Dalenda, 2010 [3] Tunisia Single site	RCT	Healthy women, GA confirmed by ultrasound GA 9-12 weeks	Mifepristone 200 mg followed 48h later by 400 mcg oral miso Misoprostol, 800 mcg, PV	**Efficacy** (mife+miso vs. miso alone): Successful abortion 40/73 vs. 28/49 Success (additional miso dose) 18/19 vs 10/10 Ongoing pregnancy: 7/73 vs 9/49 **Side effects** (mife+miso vs. miso alone): Pain 32/73 vs 35/49 Fever 4/73 vs 2/49 Diarrhea 2/73 vs 0/49 Chills 1/73 vs 0/49 Nausea/vomiting 2/73 vs 2/49 Heavy bleeding 57/73 vs 41/49 **Safety**: no cases of uterine rupture, transfusion **Acceptability** (acceptability of method; mife+miso vs miso alone): 55/73 vs 37/49	Not true randomization (by consultation date) No power calculation No repeat misoprostol in initial regimen

Table 12. Combined mifepristone misoprostol (comparisons of different regimens)

Study	Design	Inclusion criteria	Regimen/ comparison	Results	Limitations
Hamoda, 2005 [4] Scotland Single site	RCT	Healthy women aged>16 yo with singleton pregnancy, confirmed by US GA <13 weeks	Mifepristone 200 mg followed 36-48h later by: Misoprostol 600 mcg SL, q3h Misoprostol 800 mcg PV, q3h	**Efficacy 9-12 w** (600mcg SL vs. 800 mcg VL): Complete abortion 102/105 vs 84/87 Failed abortion 3/105 vs 3/87 -ongoing pregnancy 2/105 vs 0/87 **Side effects** (SL vs VL—all GA): Nausea 115/144 vs 113/146 Vomiting 104/148vs 88/144 Diarrhea 105/149 vs 74/142 **Safety** (SL vs VL- all GA): Pelvic infection 3/154 vs 2/144 Hemorrhage 2/154 vs. 0/144 on 1/154 vs 1/144 **Satisfaction** (satisfied, dissatisfied, don't know) (SL vs. VL—all GA): 108/154 vs 98/144	3 women required additional miso dose: unclear where accounted for in the data No blinding Only efficacy data disaggregated by gestational age
Chen, 2013 [5] China, 12 centers	RCT	Healthy, 18-40 yo women with singleton pregnancy, GA confirmed by US GA 8-16 weeks	Mifepristone 200mg followed 24h later by: 1. 600 mcg PV miso, q 3h 2. 600 mcg PV miso, q3h oral 3. 600 mcg oral miso, q3h 4. Mifepristone 100 mg, q 24 h x2 followed 24h later by 600 mcg miso PV, q 12h	**Efficacy**: Complete abortion (8-10 weeks): Groups 1-3 significantly more effective (about 90%) than Group 4 (about 78.2%)* Complete abortion (11-12 weeks): No differences between groups *data extracted from a figure	88 women excluded after randomization (dosing interval not respected/ one woman hypertensive) Data not extrapolated by gestational age range No blinding

Table 13. Clinic versus home use of medical abortion

Study	Design	Inclusion criteria	Regimen/ comparison	Results	Limitations
Platais, 2016[9] Kazakhstan (3 sites)	Prospective comparative trial	Women eligible for medical abortion (GA by LMP/clinical exam +/- US) GA <70 days	Mifepristone, 200mg followed 24-48h later by 600 mcg miso SL Comparison: all medications at home versus mifepristone in clinic	**Efficacy** (not disaggregated by home/clinic use): Complete abortion: 16/17(57-63 d) vs. 15/16 (64-70 d) Ongoing pregnancy 0/17 vs 1/16 **Safety:** no serious adverse events **Satisfaction** (all MA at home vs. mife in clinic): Satisfied/very satisfied 179/182 vs 101/103 **Acceptability** Choose future location of mife at home 168/182 vs 73/103	3 received additional misoprostol Side effects not disaggregated by GA or home/ clinic use Small sample size for 64-70 day gestational age range

Appendix 5: Partial list of global availability of mifepristone

BRAND NAME	STRENGTH OF MIFEPRISTONE	MANUFACTURER	COUNTRIES AVAILABLE
Abo Pill	200 mg	Cure Quick Pharmaceuticals	India
Abortab	200 mg	Bharat Serum & Vaccines Ltd	India
Cedate	200 mg	Profic Organic Ltd	India
Mifepristone	200 mg	Ba Dinh Pharmaceutical Biotech Company	Vietnam
Colestone	200 mg	Coles Pharma	India
Elmif	200 mg	Elder Pharmaceuticals Pvt Ltd	India
Empri	200 mg	Emcure Pharmaceuticals Ltd	India
Femiprevent	10 mg	China Resources Zizhu Pharmaceutical Co Ltd	Kazakhstan

BRAND NAME	STRENGTH OF MIFEPRISTONE	MANUFACTURER	COUNTRIES AVAILABLE
Fibristone	25 mg	Naari Pharma Pvt Ltd	India
Fibroease	10 mg 25 mg	Akumentis Healthcare Ltd, India	India
Ginepristone	10 mg	Stada Pharmaceuticals	Armenia, Georgia, Ukraine, Moldova, Russian Federation,
Ginestril	50 mg	Stada Pharmaceuticals	Russian Federation, Ukraine, Georgia, Moldova
Ginestril	200 mg	Stada Pharmaceuticals	Moldova
Goefibro-M	10 mg 25 mg	Koye Pharmaceuticals Pvt Ltd	India
Mediprist	200 mg	Stada Pharmaceuticals	Vietnam
Mediprist	200 mg	Acme Formulations (Pvt) Ltd, India	Uganda, Kenya

BRAND NAME	STRENGTH OF MIFEPRISTONE	MANUFACTURER	COUNTRIES AVAILABLE
Mefaprix	200 mg	Linepharma	Mexico
Mefetrac	200 mg	Fourrts Laboratories Pvt Ltd	India
Mefipil	200 mg	Abbott Healthcare Pvt Ltd	India
MFT	200 mg	Synokem Pharmaceuticals Ltd	India
MIFE - 200	200 mg	Pharbaco Central Pharmaceutical	Vietnam
Mifebort	200 mg	Taj Pharmaceuticals Ltd	India
Mifegest	200 mg	Zydus Cadila	India
Mifeprex	200 mg	Danco Laboratories	United States
Mifeone	10 mg 25 mg	Pharmanova India Drugs Pvt Ltd	India

BRAND NAME	STRENGTH OF MIFEPRISTONE	MANUFACTURER	COUNTRIES AVAILABLE
Mifegyne	200 mg	Exelgyn	Netherlands, South Africa, Sweden, Austria, New Zealand, Italy, Germany, Norway, Switzerland, Belgium, Portugal, Tunisia, Bulgaria, Greece, Romania, Cote d'Ivoire, Denmark, Russian Federation, Estonia, Finland, United Kingdom, France, Slovenia,
Mifeprin	200 mg	Sun Pharmaceutical Industries Ltd	India
Mifepristona	200 mg	Linepharma	Colombia
Mifepristone	200 mg	China Resources Zizhu Pharmaceutical Co Ltd	Uzbekistan, Georgia, Tajikistan, Kazakhstan, Russian Federation, Kyrgyzstan
Mifepro	200 mg	HLL Lifecare Limited	India
Miferiv	200 mg	East African (India) Overseas Ltd (A	India

BRAND NAME	STRENGTH OF MIFEPRISTONE	MANUFACTURER	COUNTRIES AVAILABLE
		unit of East African Remedies), India	
Mifestad 200	200 mg	Stada Pharmaceuticals	Vietnam
Mifetril	200 mg	Naari Pharma Pvt Ltd	Uganda
Miffee	200 mg	Linepharma	France, Netherlands, Barbados
Mifolian	200 mg	Shanghai New Khualian Pharmaceutical Ko Ltd	Georgia
Mifotab	200 mg	Novast	Ukraine
Mifrednor 200	200 mg	Agimexpharm Pharmaceutical JSC	Vietnam
Mifty	200 mg	Aristo Pharmaceuticals Pvt Ltd	India

BRAND NAME	STRENGTH OF MIFEPRISTONE	MANUFACTURER	COUNTRIES AVAILABLE
Miropristone	200 mg	Stada Pharmaceuticals	Georgia, Azerbaijan, Kazakhstan, Russian Federation, Ukraine, Kyrgyzstan, Moldova, Armenia
Mistone	200 mg	Novaduo Pharma	India
MTPill	200 mg	Cipla Ltd	India
Pencroftone	200 mg	Pharm Synthez (Pencroft Pharma)	Russian Federation
Pregno	200 mg	Ohm Ltd	Nepal
Pregnot	200 mg	Lupin Ltd	India
Relezed	200 mg	Zee Laboratories Ltd	India
Shiiyn	25 mg	Khubei Gedian Zenfu Pharmaceutical Co., 000	Uzbekistan
T-Pill	200 mg	Bestochem Formulations Ltd	India

BRAND NAME	STRENGTH OF MIFEPRISTONE	MANUFACTURER	COUNTRIES AVAILABLE
Termipil	200 mg	Alkem Laboratories Ltd	India
Undo	200 mg	FDC Limited	India
Unwanted	200 mg	Mankind Pharma Ltd	India
Zhenale	10 mg	Izvarino Pharma	Russian Federation
PIL'Eva	200 mg	Ba Dinh Pharmaceutical Biotech Company	Vietnam
Mifepristone Linepharma 200 mg	200 mg	Linepharma	Slovenia, Australia, Sweden, Norway, Zimbabwe, Bulgaria, Uganda, Iceland, Mongolia, Kenya, United Kingdom, Denmark, Spain, Portugal, Romania, Finland, Belgium

Source: www.medab.org, Accessed November 29, 2018.

Appendix 6: Partial list of global availability of misoprostol

BRAND NAME	MISOPROSTOL STRENGTH	MANUFACTURER	COUNTRIES AVAILABLE
Ace Miso	200 mcg	Acme Formulations (Pvt) Ltd, India	Benin, Cameroon, Niger
Apo-Misoprostol	200 mcg	Apotex Inc	Barbados, Paraguay
Cytotec	200 mcg	Pfizer Ltd	Globally, including: Slovenia, Belgium, South Africa, Benin, United Kingdom, Spain, Kenya, United States, Kyrgyzstan, Uzbekistan, Bolivia, Sweden, Lebanon, Switzerland, Lithuania, Venezuela, Burkina Faso, Cambodia, Taiwan, Malaysia, Zambia, Cameroon, Mali, Malta, Thailand, Mexico, Cape Verde, China, Togo, Myanmar, Cote d'Ivoire, Tunisia, Denmark, Netherlands, Ecuador, New Zealand, Egypt, Niger, Finland, Georgia, Nigeria, Norway, Oman, Ghana, Peru, Greece, Poland, Guyana, Portugal, Hong Kong, Iceland, Indonesia, Armenia, Ireland, Australia, Sierra Leone, Israel, Turkey, Azerbaijan, Singapore, Italy, Uganda
GYMISO	**200 mcg**	**Linepharma**	**France**

BRAND NAME	MISOPROSTOL STRENGTH	MANUFACTURER	COUNTRIES AVAILABLE
Miso-200	200 mcg	Cipla Ltd	Ghana
Miso-200	200 mcg	Naari Pharma Pvt Ltd	Congo, Dem. Rep.
Miso-Fem	200 mcg	Naari Pharma Pvt Ltd	Ethiopia, Nigeria, Liberia, Sierra Leone
Miso-Kare	200 mcg	Naari Pharma Pvt Ltd	Kenya
Misoclear	200 mcg	Acme Formulations (Pvt) Ltd, India	Ghana, Senegal, Sierra Leone, Kenya, Uganda, Burkina Faso, Malawi, Cambodia, Zambia, Mali, Tanzania
Misodel	200 mcg	Ferring Läkemedel AB	Norway, Sweden
MisoOne	400 mcg	Nordic Pharma	Spain, Switzerland, France, Italy, Latvia, Serbia
Misopro	200 mcg	Naari Pharma Pvt Ltd	Tanzania, Uganda
Misoprost-200	200 mcg	Cipla Ltd	Tanzania, Nepal

BRAND NAME	MISOPROSTOL STRENGTH	MANUFACTURER	COUNTRIES AVAILABLE
Misoprostol	200 mcg	China Resources Zizhu Pharma Co Ltd	Georgia, Russian Federation, Kazakhstan, Uzbekistan, Tajikistan
Misoprostol	100 mcg 200 mcg	AAIPharma Services Corp	Canada
Mispregnol	400 mcg	Nordic Pharma	Croatia, Czech Republic, Slovakia
PMS Misoprostol	100 mcg 200 mcg	Pharma Science Inc	Canada
Taneciprol	200 mcg	China Resources Zizhu Pharma Co Ltd	Mexico
Topogyne	200 mcg	Nordic Pharma	Russian Federation, Bulgaria, Romania, Slovenia
Vanprazol-200	200 mcg	Cipla Ltd	Nigeria

Source: www.medab.org, Accessed November 29, 2018.

Appendix 7: Partial list of global availability of mifepristone-misoprostol combi-packs

BRAND NAME	PACK SIZE	MANUFACTURER	COUNTRIES AVAILABLE
Combo	3 mifepristone and 12 misoprostol	Mife: Linepharma Miso: China Resources Zizhu Pharmaceutical Co Ltd	Mexico
Mariprist	1 mifepristone and 4 misoprostol	Acme Formulations (Pvt) Ltd, India	Zambia, Cambodia, Sierra Leone, Uruguay
Medabon	1 mifepristone and 4 misoprostol	Sun Pharmaceutical Industries Ltd	Hong Kong, Zambia, Kazakhstan, Kenya, Kyrgyzstan, Moldova, Nepal, Cambodia, Netherlands, Romania, Sweden, Czech Republic, Thailand, Denmark, Tunisia, Finland, United Kingdom, Ghana,
Mifegymiso	1 mifepristone and 4 misoprostol	Linepharma	Canada
Mifeprin kit	1 mifepristone and 4 misoprostol	Sun Pharmaceutical Industries Ltd	India
MS-2 Step	1 mifepristone and 4 misoprostol	Linepharma	Australia

BRAND NAME	PACK SIZE	MANUFACTURER	COUNTRIES AVAILABLE
Seguro	1 mifepristone and 4 misoprostol	Acme Formulations (Pvt) Ltd, India	Mozambique
Mifeso	1 mifepristone and 4 misoprostol	Acme Generics LLP	Cambodia
MariSafe	1 mifepristone and 4 misoprostol	Naari Pharma Pvt Ltd	Ethiopia
Ma-Kare	1 mifepristone and 4 misoprostol	Naari Pharma Pvt Ltd	Kenya
Divabo	1 mifepristone and 4 misoprostol	Naari Pharma Pvt Ltd	Uganda, Zambia
Safe-T Kit	1 mifepristone and 4 misoprostol	Naari Pharma Pvt Ltd	Ethiopia
MisoMife-Fem Combo	1 mifepristone and 4 misoprostol	Naari Pharma Pvt Ltd	Liberia, Sierra Leone

Source: www.medab.org, Accessed: November 29, 2018.

Appendix 8. WHO Global Abortions Policy Database: Countries with recognized approval of mifepristone, mifepristone-misoprostol and misoprostol

Table 14. Countries with recognized approval of mifepristone/ mifepristone-misoprostol

Region	Country were recognized approval (mifepristone/ mifepristone-misoprostol)
Africa	
	Benin, Burkina Faso, Cameroon, Ethiopia, Ghana, Kenya, Mauritania, South Africa, Togo, Tunisia, Uganda, United Republic of Tanzania, Zambia, Zimbabwe
Asia	
	Armenia, Cambodia, China, Hong Kong (China), India, Iraq, Israel, Maldives, Mongolia, Nepal, Tajikistan, Thailand
Europe	
	Andorra, Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Portugal, Republic of Moldova, Romania, Serbia, Slovenia, Spain, Sweden, Switzerland, Former Yugoslav Republic of Macedonia, Ukraine, UK and Northern Ireland
Latin America	
	Colombia, Mexico City, Suriname
North America	
	Canada, United states of America
Oceania	
	Australia, New Zealand

Source: Global Abortion Policies Database [online database]. Geneva: World Health Organization; 2018 (https://srhr.org/abortion-policies/). Accessed: October 30, 2018.

Table 15. Countries with recognized approval of misoprostol (WHO Global Abortion Polices Database)

Region	Country recognized approval of misoprostol
Africa	
	Benin, Burundi, Cabo Verde, Congo (DRC), Eritrea, Eswatini, Ethiopia, Ghana, Kenya, Liberia, Madagascar, Malawi, Mali, Morocco, Mozambique, Nigeria (North and South), Seychelles, South Africa, Togo, Tunisia, Uganda, Zambia, Zimbabwe,
Asia	
	Afghanistan, Armenia, Bahrain, Bangladesh, Bhutan, Cambodia, China, Hong Kong (China), Cyprus, India, Iraq, Israel, Japan, Jordan, Kyrgyzstan, Lao People's Democratic Republic, Lebanon, Maldives, Mongolia, Myanmar, Nepal, Oman, Qatar Saudi Arabia, Syrian Arab Republic, Tajikistan, Thailand, Timor Leste, Turkey, United Arab Emirates, Vietnam, Yemen
Europe	
	Andorra Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Portugal, Republic of Moldova, Romania Serbia, Slovenia, Spain, Sweden, Switzerland, Ukraine, UK and Northern Ireland
Latin America	
	Antigua and Barbuda, Argentina, Barbados, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Dominica, Dominican Republic, Ecuador, Grenada, Guatemala, Haiti, Honduras, Jamaica, Mexico City, Nicaragua, Panama, Peru, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Uruguay, Venezuela,
North America	
	Canada, United states of America
Oceania	
	Northern Territory (Australia), Queensland (Australia), Cook Islands, Fiji, Kiribati, Marshall Islands, Nauru, New Zealand, Niue, Papua New Guinea, Solomon Islands, Tonga, Tuvalu, Vanuatu,

Source: Global Abortion Policies Database [online database]. Geneva: World Health Organization; 2018 (https://srhr.org/abortion-policies/). Accessed: October 30, 2018.