CONFIDENTIAL

Mifepristone and misoprostol for the termination of pregnancy at 64-140 days since LMP

INTERNATIONAL MULTICENTRE TRIAL
ISRCTN49711898

Concept Foundation

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STUDY PROTOCOL

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1. Project summary

1.1 Justification for the project

The present project forms part of the strategy of the Concept Foundation to undertake clinical research to obtain clinical trial data for registration of medical abortion regimen beyond 63 days of gestation since LMP.

1.2 Proposed research

The proposed study is a randomized multicentre trial that will involve up to 670 pregnant women with 64-140 days of gestational age (i.e. 10^{th} – 20 weeks), in Thailand from 64-104 days (10^{th} to 14 weeks), requesting legal termination of pregnancy at clinics in India, Sweden, Thailand and Viet Nam. Eligible women who wish to join the study will first receive 200 mg mifepristone, followed either 24h or 48h later by 0.8 mg misoprostol, administered vaginally. Women will stay in the ward during misoprostol treatment, which will continue with 0.4 mg misoprostol administered sublingually 3-hourly until abortion or up to a total of 4 doses of 0.4 mg misoprostol, whichever comes first. If the woman has not aborted during the three hours following the last dose of 0.4 mg misoprostol, she will be given 200 mg mifepristone and allowed to rest for 9±2 hours after which the same misoprostol regimen (0.8 mg followed by 0.4 mg doses) will continue.

This regimen with a 36-48 h interval between mifepristone and misoprostol is recommended by the World Health Organization (WHO 2012), Royal College of Obstetricians and Gynaecologists (RCOG, 2011) in the United Kingdom and by the International Federation of Obstetricians and Gynaecologists (FIGO) when the gestational age is beyond 9 weeks (>63 days). This regimen is routinely used in many countries, although it has not been registered by any drug regulatory authorities as no pharmaceutical companies have possessed suitable data for registration.

There are several studies in the literature using this or a very similar regimen (Lokeland 2010; Hamoda 2004, 2005) and retrospective data on thousands of women e.g. from Aberdeen, Scotland. (Ashok 2004) Retrospective data from Aberdeen with 36-48 h interval using this regimen show the efficacy that is the highest ever reported, i.e. 98% complete abortion rate up to

12 weeks and after 12 weeks up to 97% abortion rates (prof. A. Templeton, personal communication).
The aim of this study is to collect data on efficacy, side effects and complications, while using this regimen to induce abortion.

1.3 New features

This is the first clinical trail that uses the same misoprostol regimen in pregnancies of 64-140 days' gestation until abortion and comparing the 24h and 48h intervals between mifepristone and misoprostol administration throughout these gestational weeks.

1.4 Techniques and skills

The study requires the clinical facilities and expertise to carry out pregnancy termination and investigators who have prior experience with abortions induced medically.

1.5 Problems anticipated

Apart from the logistical problems related to the setting-up and co-ordination of this multicentre trial, no difficulties are envisaged.

2. Description of the project

2.1 Rationale and objectives of the study

2.1.1 Rationale

The evidence-based regimen of medical abortion for gestations of 64-84 days in WHO guidelines of 2012, is: 200 mg mifepristone followed 36-48h later by 0.8 mg misoprostol vaginally and then continued by 0.4 mg misoprostol every 3 hours up to four additional doses given either vaginally or sublingually (see Annex A).

Several studies demonstrate that in later gestations it is important to give the first dose of misoprostol vaginally as it seems to have an additional priming effect on the cervix and the plasma levels stay high longer, i.e. for up to 6 hours, compared to administration via other routes.

Pharmacokinetic studies in Hong Kong (Tang, 2009) show that as soon as bleeding has started, absorption of vaginally administered misoprostol is significantly reduced. This is why sublingual administration of subsequent doses has been shown to give a better efficacy (Templeton A; personal communication). The peak plasma levels of successive doses of sublingual misoprostol are similar, so there is no accumulation of misoprostol with 3 h administration intervals as demonstrated in a study by Tang et al. (2009).

After sublingual administration the increase in uterine tonus is more rapid and more pronounced than after vaginal administration, but the contractions start to decrease after about 3 hours compared to 4-5 hours after vaginal dose (Aronsson, 2004). Diarrhoea, fever and chills have been the most common side-effects after sublingual administration (von Hertzen, 2007). The regimen has been shown to be acceptable to women, as almost all women who have a complete abortion would choose this method again, and the sublingual route was regarded as convenient and as giving more privacy during the abortion process (Hamoda, 2005).
The results of studies in the second trimester demonstrate a somewhat better efficacy, a shorter induction to abortion interval and less pain when the interval between mifepristone and misoprostol is 36-48h compared to 24h interval. This seems to be the case especially in later gestations, i.e. after 16 weeks (Mentula, 2011). However, no studies until now have compared the 24h and 48h intervals in the late first trimester (64-104 days).

In a study by Mentula et al. 227 women undergoing pregnancy termination at 13-24 gestational weeks were randomized to start misoprostol administration (0.4 mg every 3 hours) either one or two days after mifepristone. In intention-to-treat analysis, the median induction-to-abortion interval was 1h longer in the one-day group (8.5 versus 7.2 h, P = 0.038), but in per-protocol analysis, the rate of surgical evacuation was higher in the 2-day group [30/115 (25%) versus 40/112 (37%); 95% confidence interval 0.3-24.1, P = 0.044]. A subgroup analysis showed that the median induction-to-abortion interval was 3h longer in the one-day group amongst women without previous vaginal deliveries (10.1 versus 7.6, P = 0.013) and when gestation exceeded 16 weeks (10.8 versus 7.2, P = 0.024).

A retrospective cohort study of 127 women, with gestation between 13 and 24 weeks, compared also the effect of a 1-day and a 2-day interval between 200 mg of oral mifepristone and 0.4 mg vaginal misoprostol administered every 3 h. The time to fetal expulsion was longer (9.8 versus 7.5 h; $p<0.01$) in the 1-day than in the 2-day group, but the median number of misoprostol doses was identical and abortion occurred in 98% within 24 h in both groups. The time to abortion was

longer in women with a gestation of 17-22 weeks compared to women with lower gestation (10.2 versus 6.8 h; $p<0.001$). The authors concluded that the interval between the drugs can be reduced allowing individualised patient care (Nilas, 2007).

Although the 36-48h-regimen is 'the gold standard' and recommended by several guidelines and routinely used in many European countries, it has not been licensed in any country. Due to its efficacy and safety, medical abortion with mifepristone and misoprostol should be promoted and included in national guidelines in countries that use less effective and outdated methods. Registration would give justification for its use and avoid off-label use of these drugs at the proposed gestations. If the 24h-regimen is proven to be non-inferior to the 48h-regimen, then it could be recommended in settings where it is more convenient for women to return for misoprostol administration one day rather than two days after mifepristone.
In the present randomized trial we evaluate the effects of starting misoprostol treatment either 24h or 48 h after mifepristone administration. As our first dose of misoprostol is 0.8 mg compared to 0.4 mg in the above studies and as we continue with sublingual misoprostol, which may be more effective especially when there is vaginal bleeding, we may see better results in both arms compared to previous studies.
It would give flexibility for clinical practise if both 24h and 48h intervals could be used and registered for the medical abortion regimen beyond 63 days.

2.1.2 Objectives

The ultimate goal of this research is to collect data for registration of a medical abortion regimen for pregnancies of 64-140 days since LMP. Specifically, to investigate whether both 24h and 48h intervals between mifepristone and misoprostol give similar expulsion rates, accepting a difference of up to 5% at 24 h, to justify the use of both intervals in clinical practise.

The data will be analysed for the 24h and 48 h interval groups to compare them with regard to the following

(i) the efficacy to induce abortion at gestations between 64-104 days LMP (= first trimester - according to WHO guidelines first trimester of pregnancy is up to 104 days LMP; see Annex A) and between 105-140 days LMP;
(ii) the rate of complete abortion between 64-104 days and 105-140 days;
(iii) the induction-to-abortion interval between 64-104 days LMP and 105-140 days LMP;

(iv) the occurrence of side-effects; and

(v) women's perceptions.

2.2 Efficacy estimation and hypothesis

The retrospective data on thousands of women e.g. from Aberdeen show a high efficacy, abortion rate of 97% at 24 hours after the start of misoprostol administration, for the 36-48h regimen. Our hypothesis is that the 24h regimen is non-inferior in efficacy, measured as the abortion rate (fetal expulsion) at 24 h, to the 48h regimen, assuming that this rate in both interval groups will be about 96% to 97%, and within an inferiority margin of 5%.

2.3 Previous similar studies

Several studies have shown the efficacy of 200 mg mifepristone followed 36-48 hours later by 0.8 mg misoprostol when continued by 0.4 mg misoprostol either orally, vaginally or sublingually.

The rate of *complete* abortion was 91.7% in a study by Lokeland et al. in Norway when the initial vaginal 0.8 mg dose was followed by repeated oral doses of 0.4 mg misoprostol in gestations of 64-84 days among 254 women. A retrospective review of 1076 consecutive cases reported by Hamoda et al.(BJOG 2005) at 9-13 weeks' gestation showed decreasing rates of *complete* abortion from 97.3% at 64-70 days to 94.9% at 78-84 days and 92% at 85-91 days.

Retrospective data from Aberdeen on 10,291 women (Prof. Allan Templeton; personal communication) shows that the rate of *complete* abortion decreases with increasing gestation from 98.3% at 8-9 weeks to about 95.9% at 20 weeks' gestation, and the occurrence of heavy bleeding requiring emergency curettage increases from 0.4% at 8-9 weeks to 1.1% -1.8% at 20 weeks. This is why women with gestations beyond 63 days are usually treated inside the clinic until after abortion.
These data showed that in late first trimester most women, i.e. about 75%, abort within 6 hours after the start of misoprostol administration. In later gestations the mean time to abortion is about 6-7 hours.

Ashok et al. (Contraception 2004) assessed the effectiveness, safety and factors that affected the outcome of mid-trimester medical termination of pregnancy at 13-21 weeks gestation in Aberdeen, Scotland, using 200 mg mifepristone followed 36-48 h later by 0.8 mg vaginal

misoprostol and then continued with 0.4 mg misoprostol either vaginally or orally. Of the 1002 women, three took mifepristone and decided to continue with the pregnancy, with 999 women being compliant with the regimen. Of these, 2 women aborted prior to administration of misoprostol and 970 (97.1%) women had a successful expulsion within five doses of misoprostol, and surgical intervention was necessary to complete the abortion process in 81 (8.1%) women.

Women with no previous pregnancy ($p = 0.02$), no previous live birth ($p = 0.0001$) and gestations 17-21 weeks ($p = 0.001$) required more prostaglandin. Younger women ($p = 0.0001$) and women with a previous live birth ($p = 0.001$) were more likely to have a successful abortion. The induction-to-abortion interval was significantly longer with increasing gestation [95% confidence interval (CI) difference in means: -2.52 to -0.89, $p = 0.0001$], increasing age ($p = 0.0001$) and no previous live birth (95% CI difference in means: -0.25 to -1.01, $p = 0.0001$). Surgical intervention was more likely to be required with increasing age ($p = 0.008$).

The authors concluded that mifepristone in combination with misoprostol is a safe and effective regimen for midtrimester medical abortion, with younger women and those with a previous live birth more likely to have a successful abortion.

2.4 Design and methodology

2.4.1 General outline

This study will be a multicentre, randomized, clinical trial including up to 670 women with pregnancies of 64-140 days from last menses (verified by ultrasound) recruited for the study at participating centres: 75 in Chandigarh, 75 in Gurgaon, NCR, 200 in Hanoi, 200 in Bangkok and Khon Kaen (for 64-104 days LMP only) and 120 in Stockholm from among women requesting legal termination of pregnancy and who are eligible and choose medical abortion. All women will get 200 mg mifepristone orally, and are randomized to be hospitalized either 24h or 48h later, when they receive 0.8 mg misoprostol vaginally. The treatment will continue with 0.4 mg misoprostol administered sublingually at 3h intervals up to four doses of 0.4 mg or until abortion, whichever occurs earlier.

In rare cases when the women has not aborted with these five misoprostol doses (0.8 mg plus 4 x 0.4 mg), an additional dose of 200 mg mifepristone will be administered 3 h after

the last misoprostol dose, and the misoprostol treatment (0.8 plus 0.4 mg doses) will continue the next morning around the same time as day before.

Side-effects will be recorded each time before a new dose of misprostol is administered. The preliminary outcome will be assessed before the woman leaves the clinic. The final outcome regarding the efficacy, side-effects since treatment and acceptability will be assessed at the follow-up visits on Day 14-15 of the study. If the woman is still bleeding a further follow-up may be considered.

2.4.2 The centres participating in this trial

This multicentre, randomized clinical trial will be carried out in hospitals in India (PGIMER, Chandigarh, and Fortis Memorial Research Institute, Gurgaon, NCR), Viet Nam (NHOG, Hanoi), Sweden (Karolinska Hospital, Stockholm) and Thailand (Ramathibodi-, Siriraj- and Chulalongkorn hospitals, Bangkok, and Health Promotion Hospital, Khon Kaen). All these hospitals are already providing medical abortion services and also carry out clinical research. The trial will be conducted according to ICH-GCP guidelines and the investigators are trained to carry out research accordingly.

2.4.3 Criteria for the selection of subjects

A total of up to 670 women (at least 600) (75 estimated in Chadigarh, 75 in Delhi, 200 in Hanoi, 120 in Stockholm and 200 in Bangkok and Khon Kaen) will be recruited from among women requesting legal termination of pregnancy. Participants will satisfy the following criteria:

(a) Criteria for inclusion

Subjects admitted to the study will fulfil all of the following criteria:

- good general health
- older than the age of legal consent
- requesting abortion and eligible for legal termination of pregnancy
- on Day 1 of the study (day of mifepristone administration) the duration of pregnancy between 64-140 days, - 64-104 days LMP in Thailand - , verified by ultrasound
- the pregnancy is single and intrauterine (single sac)

- if treatment with the proposed regimen should fail agrees to be treated with the method used at the clinic routinely in this kind of cases
- willing and able to participate after the study has been explained
- haemoglobin higher than 90 g/l.

(b) Criteria for exclusion

Any indication of serious past or present ill health will be considered a contraindication for recruitment to the study.

In particular, subjects should not be recruited if any of the following conditions is present:

- allergy towards mifepristone or misoprostol
- history or evidence of disorders that represent a contraindication to the use of mifepristone (chronic adrenal failure, severe asthma uncontrolled by corticosteroid therapy, inherited porphyria) or prostaglandins (mitral stenosis, sickle cell anaemia, uncontrolled hypertension, systolic blood pressure lower than 90 mmHg measured with a traditional instrument)
- a history or evidence of thrombo-embolism, severe or recurrent liver disease
- has a medical condition or disease that requires special treatment, care or precaution (e.g. corticosteroid or anticoagulant therapy) in conjunction with abortion
- the presence of an IUD in utero
- previous surgery of uterus/uterine cervix is a relative contraindication. However, one previous low-segment caesarean section does not need to be a contra-indication
- molar pregnancy or threatened abortion
- in case difficulties are anticipated in the follow-up of the woman.

Women older than 35 years can be recruited for the present trial provided they do not smoke, their diastolic blood pressure is < 90mmHg and have no known risk factors for cardiovascular disease.
Women who breastfeed can be included but they may discard the breast milk on the day of mifepristone administration.

(c) Criteria for exclusion from per-protocol analysis

The main efficacy analysis will include all women randomized for whom outcome is known (see item 2.4.11). Criteria for exclusion from per-protocol analysis are the following:

- essential data are missing from the participant's records making it impossible to judge treatment outcome (same as for main analysis).
- any violation of the study protocol, including violation of eligibility criteria
- treatment non-compliance

2.4.4 Subject allocation

Women are eligible for the study if they satisfy all the inclusion criteria and do not have any of the conditions described as criteria for exclusion.

1) Day 1 of the study: women will be randomized to 24h interval or 48h interval and they will receive one tablet of 200 mg of mifepristone orally; and
2) 24h or 48 h later: women will be hospitalized and they will be given 4 tablets of 0.2 mg misoprostol vaginally.
Even if the woman aborts already after mifepristone, before administration of misoprostol, she should be given the first dose of misoprostol.

3 hours later two tablets of 0.2 mg misoprostol will be administered sublingually, unless the woman has already aborted, and the treatment will continue with the same dose at 3-hourly intervals up until four doses of two tablets of 0.2 mg misoprostol have been administered or until abortion, whichever comes earlier.
If the woman has not aborted 3 hours after the 4^{th} dose of 0.4 mg misoprostol, again 200 mg mifepristone is administered orally and the misoprostol treatment is resumed in the morning starting with 0.8 mg dose vaginally.

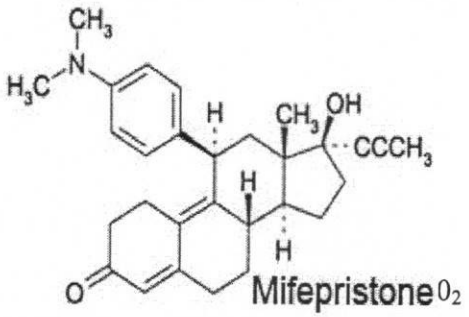
The mifepristone and misoprostol tablets are in aluminium blisters. Each participating woman will get the mifepristone tablet and the four tablets of 0.2 mg misoprostol from the Medabon® blister. Additional misoprostol will be provided to the participating hospitals for the administration of subsequent doses of misoprostol as needed.

2.4.5 Description of the drugs to be studied

(i) Mifepristone (Sun Pharmaceuticals Ltd. Mumbai, India)

(a) Chemical name: 17β-hydroxy-11β-[p-(dimethylamino)phenyl]-17-(1-propynyl)estra-4,9-dien-3-one

(b) Chemical structure:



Mifepristone 0_2

(d) Route of administration: oral tablets

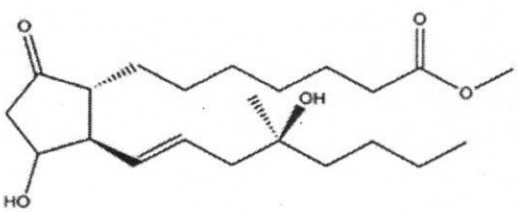
(e) Amount present per tablet: 200 mg

See investigators Brochure for further information

(ii) Misoprostol (Sun Pharmaceuticals, Mumbai, India)

(a) Chemical name:
(±)-methyl(1R,2R,3R)-3-hydroxy-2-[(E)-(4RS)-4-hydroxy-4-methyl-1-octenyl]-5-oxycyclopentaneheptanoate

(b) Chemical structure:



(c) Empirical formula: C_{22} H_{38} 0_5

(d) Route of administration: oral tablets (for sublingual or vaginal use in the study)

(e) Amount present per tablet: 200 µg.

See Investigator's Brochure for further information.

2.4.6 Study procedure

2.4.6.1 Admission to the study:

Before admission potential subjects will undergo the following:

- ultrasound examination to verify the length of the pregnancy and check that the pregnancy is intrauterine. If the pregnancy is more advanced, if there is a suspicion about an extra-uterine or molar pregnancy, the woman will not be admitted to the study.
- haemoglobin measurement
- the blood group and Rh typing according to the routine of the centre
- full medical, obstetrical and gynaecological history
- full medical and gynaecological examination including pelvic examination, height, weight and blood pressure
- bacteriological examination according to the routine of the centre

Women who fulfil the criteria for admission [see 2.4.3 (a) and (b)], and who are willing and able to participate in the trial and have given their informed consent will be included in the study.

Subjects admitted to the study will be given a diary card to record days and amount of vaginal bleeding and side-effects. The card will also give the date of hospitalization for misoprostol administration as well as the date of the follow-up visit. The day of start of the treatment will constitute the day of formal admission to the study (i.e. Day 1 of the study) when the length of pregnancy should be 64 to140 days (64 to 104 days in Thailand).
The envelope with the next subject number will be opened to see whether misoprostol treatment will start 24h (Group A) or 48h (Group B) after mifepristone administration. The mifepristone tablet must be swallowed in the presence of a member of the study team who will record on the data form the date and time when the tablet was taken.

2.4.6.2 Visits to the clinic and assessment of treatment outcome:

Misoprostol treatment in hospital and follow-up

After the admission visit on Day 1 all subjects will attend the clinic on two occasions during the course of the study.

(a) Day 2 or 3: misoprostol treatment on the hospital ward

- physical examination (general status, RR, palpation of abdomen, auscultation of heart and lungs)
- administration of 4 tablets of misoprostol vaginally in the ward
  followed by a 3-hour clinical observation period (pain killing may be provided prophylactically after misoprostol administration); prior to the administration of the next dose possible side-effects and any medications given during the last 3 hours will be recorded
- both the times of tablet administration and of foetal expulsion and expulsion of the placenta, if they occur, will be recorded on the data forms. If placenta has not expelled, an additional dose of 0.4 mg misoprostol will be given.
- observation in the clinic for 2-3 hours after expulsion
- vaginal examination before leaving the clinic, if indicated
- blood sample for haemoglobin (if felt necessary due to heavy bleeding)

(b) Day 14±2 (follow-up visit)

- medical interview and review of diary card
- physical and pelvic examination if felt necessary
- ultrasound examination, etc. if judged necessary from clinical findings.

2.4.7 Assessment of the outcome of treatment

The primary outcome is the efficacy of the treatment in achieving termination of pregnancy. This will be known before the woman leaves the clinic. In addition, the following outcomes will be analysed: rate of complete abortion; induction-to-abortion interval; the occurrence of side-effects and complications; and women's perceptions about the treatment.

a) Efficacy

The initial judgment about the outcome of therapy is made at the clinic before discharge home. The outcome is classified on the basis of the subject's history and the clinical findings, and if necessary, at ultrasound (US) examination, as

1) complete abortion - no additional treatment needed for foetal and complete placental expulsion - uterus empty

2) incomplete abortion - VA or curettage done due to remnants of tissue in uterus
3) missed abortion - no expulsion; remaining intrauterine sac without heart beats
4) failed termination of pregnancy - live pregnancy, heart beats seen in US
5) undetermined, including vacuum aspiration on woman's request or when indicated for other reasons before the outcome of this treatment can be assessed.

The main outcome is abortion (foetal expulsion), whether complete or incomplete, considered as successful treatment outcome, while treatment failures will include missed abortion, continuing pregnancy and undetermined outcomes.

Even if the woman aborts already after mifepristone, before administration of misoprostol, she should be given the first dose of misoprostol.

The final outcome will be determined based on the findings at the Day 14±2 follow-up visit. If no emergency or elective curettage, or additional misoprostol, was necessary during the follow-up period, the outcome of treatment is classified as "complete abortion". If the clinical findings are compatible with "incomplete abortion", two misoprostol tablets can be administered sublingually, if the pregnancy was up to 12 weeks (90 days), or vacuum aspiration can be performed. In later gestations vacuum aspiration/uterine evacuation will be performed if abortion is incomplete as well as in case of heavy bleeding or suspected infection. These cases are classified as "incomplete abortion". If the women discontinues the treatment and has vacuum aspiration/evacuation before the outcome is known, the outcome will be regarded as "undetermined".

b) Induction-to-abortion interval

Induction-to-abortion interval is the time in hours from the start of misoprostol administration until the expulsion of the foetus. If the woman aborts before misoprostol administration, the time to abortion will be negative.
According to previous experience up to two thirds of the expulsions take place in the clinic during the first six- to eight hour- observation period after misoprostol administration. The time of expulsion will be recorded on the data collection forms.

c) Incidence of side-effects

Signs and symptoms will be recorded at admission and women will keep daily records of any complaints and medication taken for the duration of the whole trial and report them at each visit. Data on signs and symptoms will be collected prior to misoprostol administration for the previous 3h interval. The pain is recorded using the scale from 0-10, in which 0 means no pain and 10 is the worst possible pain the subject can imagine.

We classify the signs and symptoms that women may have during the trial as follows:

1. Pregnancy-related symptoms: such as nausea, vomiting, breast-tenderness, fatigue, dizziness, headache and fainting;
2. Drug-related side-effects, such as diarrhoea, fever and rash;
3. Side-effects related to the abortion process, such as lower abdominal pain and bleeding; and

d) Women's perceptions

Women's perceptions on the treatments are assessed at the first follow-up visit using slightly modified versions of the questionnaires from previous trials.

2.4.8 Criteria for discontinuation

3.4.8.1 Of individual subjects in the study

An individual subject's participation in the study is discontinued if she wants to withdraw her participation or is lost to follow-up.

Side-effects such as nausea, vomiting, uterine pain, etc. that may occur in some women during the course of induced abortion do not constitute a reason for discontinuation and will be treated symptomatically where necessary.

2.4.8.2 Of the study itself

As this is a reasonable small study we do not nominate any independent data safety monitoring board (DSMB). Also, there is a lot of experience on the use of the study regimen so it is unlikely that there is any need to discontinue the study due to treatment not being effective or for any other reasons.

If any investigator is worried about any symptoms related to the treatment (s)he has to inform the Concept Foundation immediately.

2.4.9 Laboratory and other investigations

Pre-admission tests, such as the blood group and Rh typing (see item 2.4.6) and haemoglobin measurement (Days 1) will be carried out by methods routinely employed at each centre. Ultrasound examinations will be done to verify the length of the pregnancy before admission and, if judged necessary from clinical findings, any time during the study.

2.4.10 Data management

A computer-generated randomisation sequence will be produced centrally in Chulalongkorn University, Bangkok, to assign participants within each centre to receive misoprostol 24h or 48h after mifepristone. The randomisation will use randomly permuted blocks and the sequence will be kept concealed from the staff at Concept Foundation and the trial investigators. Participating centres will be requested to record the data on paper data collection forms, enter them and send them electronically on a weekly basis using a Web-based system developed by a statistical consultant to Concept Foundation. Recruitment and data quality will be monitored by the staff of the Concept Foundation and the statistical consultant using this system.

2.4.11 Data analysis

Data will be analysed centrally in Chulalongkorn University in Bangkok.

Baseline

Descriptive statistics will be calculated for all baseline characteristics for all subjects randomized, by treatment group, to describe characteristics of the population and to assess comparability of the groups. The overall summary statistics for women who complete the trial will be compared with those for the subjects lost to follow-up.

Efficacy of the treatment

All subjects randomized having known primary outcome (foetal expulsion) will be included in the main efficacy analysis in their randomized groups. If attempts fail to locate and contact a

woman lost to follow-up, and her final outcome of treatment is not known (complete or incomplete abortion), then that woman will be excluded from the first efficacy analysis.

Crude rates for each outcome will be calculated in each arm and exact confidence intervals based on the binomial distribution calculated as described in Armitage and Berry (1994).

To establish the non-inferiority of the 24h regimen compared to the 48h regimen regarding efficacy, we will require the upper limit of the 95% confidence interval for the difference (48h-24h) in abortion rates to be below the margin of equivalence of 5%.

The analysis of abortion rates will be conducted using logistic regression, adjusted by centre and for any prognostic variable showing imbalance at baseline.

Additionally, relative risks will be computed to compare treatment failures between the groups. Interactions between treatment and centre, treatment and gestational age and treatment and parity will be assessed with a logistic regression model. If an interaction is significant at the 10% level, a stratified analysis will be considered. Stratified analysis by gestational age would be conducted using the groups 64-104 days (first trimester) and 105-140 days (second trimester). Stratified analysis by parity will use the groups parous and non-parous.

A per-protocol analysis will be performed excluding women with conditions described in section 2.4.3 (c). Efficacy will also be calculated excluding subjects with undetermined outcome.

Induction-to-abortion interval

Time to fetal expulsion will be computed and then analysed using standard survival analysis techniques. For this analysis, women with treatment failure will be considered censored with censoring time equal to the time from onset of treatment to surgical termination of the pregnancy. Median times to expulsion will be derived from Kaplan–Meier estimates of the survival function, and treatment groups will be compared using the log-rank test. Interactions between treatment and centre and treatment and parity status will be assessed using the Cox regression model. Comparisons of side effects and women's perceptions on the regimens will be carried out using Fisher exact tests.

Side-effects

Mantel Haenszel chi-square test or Fisher exact test as appropriate, will be used to compare the proportion of women with each side-effect, adjusting for multiple inferences with an appropriate technique.

2.4.12 Number of subjects and statistical power

To establish the non-inferiority of the 24h regimen compared to the 48h regimen regarding efficacy, we will require the upper limit of the 95% confidence interval for the difference (48h-24h) in abortion rates to be below the margin of non-inferiority of 5% with a power of 80%. If the abortion rates in the two regimens are both equal to 96%, 242 women will be required for each group, a total of 484, or about 500, which will be the minimum number of women recruited for this study. However, the centres may continue to enrol more women up to their individual target numbers, i.e. up to a total of 670 women. We anticipate no loss to follow-up for this non-inferiority outcome because the abortion rate will be observed before discharge from hospital.

2.4.13 Duration of project

It is estimated that the trial will require 12 to 14 months for data collection at each centre and between 6 and 12 months of centralized data analysis in Thailand.

2.5 Project management

The trial will be conducted in four countries under the supervision of a principal investigator in each centre. The responsibilities of principal investigators are described in the "Guidelines for Investigators" for this project.

Overall co-ordination of the project will be the responsibility of the Concept Foundation's staff and statistical consultant nominated for the study. This is responsibility will include, inter alia, the organization and supervision of the trial, communication with the principal investigators, and the analysis and writing-up of the results.

2.6 Links with other projects

Over the past few years Concept Foundation has carried out introductory studies in Thailand and Viet Nam on the use of misoprostol after mifepristone pre-treatment for termination of early pregnancy.

2.7 Main problems anticipated

No major problems are anticipated as the centres selected have previous experience on studies and collaboration in this area with WHO and/or Concept Foundation.

2.8 Expected study outcomes

If the results of the study suggest similar efficacy the study is likely to contribute to registration of the regimen with both 24h and 48 h intervals between mifepristone and misoprostol administration. This will allow more flexibility in the clinical practice.
As per usual practice, the results of this multicentre trial will be submitted for publication in a peer-reviewed scientific journal, and a summary of the findings will be published on Concept Foundation's and on Medabon web-site.

Following acceptance of the manuscript with the overall trial results, individual investigators may publish their own centre's data in local journals, if they wish, provided such publications make reference to the publication with the overall results and the manuscript has been approved by Concept Foundation.

Information from this study will be of value to practitioners using mifepristone and misoprostol for the termination of pregnancy and, depending on the trial's outcome, may result in modifications of the treatment regimens currently in use.

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4. Ethical considerations

Note: Ensure all information requested in the corresponding section of Part 1 is provided

4.1 Informed consent and confidentiality

At centres that provide both medical and surgical methods of abortion, the women who choose medical abortion are informed of the study and invited to join it. In centres where medical abortion is only being provided in the context of the study, women are informed of the procedure normally available (surgical abortion and what it entails) and then invited to take part in the

study. All potential volunteers will be informed about the aims and protocol of the study, side-effects that may occur as a result of the treatment, and the alternative method(s) of pregnancy termination that is (are) available. It will be explained to them the measures taken to ensure confidentiality and their right to withdraw from the study at any time without prejudice to their further medical care. Women participating in the study will be asked to sign the consent form of Annex B. Where necessary, this form will be translated by the principal investigator into the subject's own language, and additions made to it as dictated by local requirements and the laws of the country.

As per usual practice, subjects will be identified by number only on all data forms and correspondence.

4.2 Risk-benefit assessment

Experience gained so far with the use of mifepristone followed by misoprostol for the termination of pregnancy indicates that this therapy has side effects and a frequency of short-term complications comparable to that observed after vacuum aspiration. The most common complaint during treatment is lower abdominal pain, which results from uterine contractions and the abortion process itself. This is felt by practically all women. WHO study demonstrated (Project 97903) using vaginal misoprostol that pregnancy related symptoms such as breast-tenderness, nausea and vomiting decrease during treatment from 46% to 18%, from 60% to 16% and from 27% to 5%, respectively. About 5-7% of women had diarrhoea and about 5% had shivering/fever during the procedure. Less frequent side effects include dizziness, headache and rash. Side effects occur usually within the first 2 hours after misoprostol and are of low intensity, except of pain which requires treatment in about half of the cases.

Subjects will be informed about possible complications, and centres participating in the trial will take the necessary measures to ensure that qualified personnel and facilities are available at all times to deal with them.

Most women participating in the study can be expected to have a complete abortion and will not be exposed, therefore, to some of the risks associated with vacuum aspiration, particularly the risks of physical trauma (cervical laceration, uterine perforation, etc.). Even if surgical intervention is needed it is likely to be easier as the treatment has dilated and softened the cervical canal.

No financial incentives will be offered to potential study participants and no financial remuneration will be given to women recruited into the study, other than reimbursement of expenses incurred as a result of participating in the study (travel expenses for extra hospital visits due to participation in the study; lost working hours; etc.).

Annex A

Extracts from WHO Safe Abortion guidelines 2012

Table 1. Equivalent gestational ages in weeks and days during the first trimester

Weeks of gestation	Days of gestation
<1	0–6
1	7–13
2	14–20
3	21–27
4	28–34
5	35–41
6	42–48
7	49–55
8	56–62
9	63–69
10	70–76
11	77–83
12	84–90
13	91–97
14	98–104

Adapted from: ***International statistical***

World Health Organization. Safe Abortion: technical and policy guidance for health systems. Second edition. Geneva 2012:

Recommended methods for medical abortion:

The recommended method for medical abortion is mifepristone followed by misoprostol.

For pregnancies of gestational age between 9 and 12 weeks (63–84 days)
The recommended method for medical abortion is 200 mg mifepristone administered orally followed
36 to 48 hours later by 800 μg misoprostol administered vaginally. Subsequent misoprostol doses should be 400 μg, administered either vaginally or sublingually, every 3 hours up to four further doses, until expulsion of the products of conception.

For pregnancies of gestational age over 12 weeks (84 days)
The recommended method for medical abortion is 200 mg mifepristone administered orally followed 36 to 48 hours later by repeated doses of misoprostol.

With gestations between 12 and 24 weeks, the initial misoprostol dose following oral mifepristone administration may be either 800 μg administered vaginally or 400 μg administered orally.

Subsequent misoprostol doses should be 400 μg, administered either vaginally or sublingually, every 3 hours up to four further doses.

For pregnancies beyond 24 weeks, the dose of misoprostol should be reduced, due to the greater sensitivity of the uterus to prostaglandins, but the lack of clinical studies precludes specific dosing recommendations.

Annex B

Here a copy of the consent form and information sheet as drafted for the centre.

INFORMATION TO POTENTIAL PARTICIPANTS IN A STUDY

entitled

"Mifepristone and misoprostol for the termination of pregnancy at 64-140 days since LMP"

Study code…

Our hospital is participating in a study that collects information for registration of two drugs, mifepristone and misoprostol, for the termination of pregnancies of 10-20 weeks' duration. This same study is being carried out in eight hospitals in India, Sweden, Thailand and Viet Nam (CORRECT AS RELEVANT IN YOUR COUNTRY)

We give you here some information about the study so that you can decide if you wish to join it. We are also willing to answer any questions that you may have about this study.

Background
Pregnancy can be terminated by using two drugs, mifepristone and misoprostol. This method is already available since 25 years and it is recommended as 'the gold standard' by the World Health Organization. These drugs can be used, and are being used, to terminate the pregnancy at any stage. However, they are currently registered to be used in pregnancies of up to 9 weeks only, as there are no suitable studies in later pregnancies that could be used for registration. This is why we are undertaking this study to collect information for registration in pregnancies that are more than 9 weeks' duration.

How do these drugs work?
Mifepristone, the first drug, stops the pregnancy to grow. The second drug, misoprostol, which is taken one or two days later, causes contractions in the uterus, which lead to the expulsion of the pregnancy. You may feel cramp-like abdominal pain similar to that occurring in painful periods. Some women may have headache and nausea, and sometimes vomiting and diarrhoea after misoprostol.

Purpose of the study
We expect that this study will show how effective these two drugs are in terminating pregnancies of 64-140 days or 10-20 weeks' duration (64-104 days, 10-14 weeks, in Thailand). We also investigate if the one day and two day-intervals between the administration of mifepristone and misoprostol give similar results.

Procedures in the study
We will ask you some questions and investigate the length of your pregnancy to ensure that you can participate in this study. We do not use your name in any documents but give you a participant number so that your identity remains unknown to everybody except the doctors and nurses in this hospital who look after you.

During the study we will ask you some questions: first when you are admitted to the study, then when you get the second drug, misoprostol, in the hospital, and the last time when you come for the follow-up visit about two weeks after abortion.

After you agree to join this study, you will get one tablet of mifepristone which you will swallow, and after about a half an hour you may go home. The next day you may feel some light contractions in the uterus and sometimes there is some bleeding. However, bleeding does not mean that the pregnancy is

terminated, so you will need to come to the hospital for the administration of the second drug, misoprostol. A half of the women in the study will come to the hospital one day after the first drug and another half two days after the first drug. Whether you will come to the hospital one or two days later depends on the chance, and we will tell you when you will come after you have taken the first drug.

During the administration of the second drug you will have to stay in the hospital. You may get several doses of this second drug depending on how long it will take for the pregnancy to be terminated. Most commonly it takes about 6-7 hours.
The nurse will give the first dose, four small pills, into your vagina. You may feel pain 30-60 minutes later as this drug causes the uterus to contract to expel the pregnancy. You will be given pain killers when needed.
Further doses of these tablets are given under your tongue, two pills at each time at 3-hour intervals until abortion. You should keep these tablets under the tongue for about 10 minutes until they melt. However, before we give you a new dose of these tablets the nurse will discuss with you and see that you are well.

If you have not aborted with five doses of this second drug, you will be given again one tablet of the first drug to swallow after which you may rest for the next 9-11 hours. In very rare cases we may need to repeat the treatment next day with the second drug.

After abortion you will stay a few hours in the hospital as we wish to make sure that you are well and can safely leave and go home.
You will have some bleeding for about two weeks and you may feel occasionally some contractions. You will come for a follow-up visit to the hospital two weeks after abortion so that we can ensure that all is fine with you.
However, you can come to the hospital at any time if you have problems. We will give you a list of situations when you have to come right away to the hospital.

Risk and discomforts
Participation in this study will not increase your risk of complications from termination of pregnancy. Mifepristone and misoprostol are safe drugs. However, misoprostol can cause stomach cramps, nausea and headache, more seldom vomiting and diarrhoea. In rare cases there may be a heavy bleeding associated with abortion, but the nurses and doctors taking care of you know to treat this.

Benefits
Using the two drugs for the termination of pregnancy you will avoid possible risks and complications from using a surgical method.
Moreover, your participation in this study will help to collect information that will be used for making this method available in your country and many other countries around the world so that also other women can benefit from this method of pregnancy termination.

Compensation
You will be reimbursed of expenses incurred as a result of participating in the study i.e., ultrasound examination, vaginal examination, medical abortion regimen for termination of pregnancy, and in-patient hospital stay. (TO BE MODIFIED ACCORDING TO THE SITUATION IN THE COUNTRY)

Alternatives to participation
Your participation in this study is completely voluntary. Instead of participating, you may choose the usual method for termination of pregnancy in this hospital i.e. (PLEASE EXPLAIN THE ALTERNATIVES HERE).

You have the right to withdraw from the study at any time without prejudice to your further medical care. However, if you have already taken the first study drug, we recommend that you complete the treatment, as we do not know the effect of the drug on the foetus.

Participation and personal information in this study will be kept confidential. Authorized people or relevant authorities monitoring, auditing or inspecting the conduct of the study may have access to

personal information provided by women participating in the study. People monitoring, auditing or inspecting the study are duly bound to treat any information about women participating in the study as confidential. By signing the information consent form you are consenting to such review and disclosure.

In this clinic the doctor in charge of this study is:.....
Telephone number to contact:.....

I, ...(full name of subject)
..... (full address of subject) have read/understood (delete as appropriate) the information about this study that was given/read (delete as appropriate) to me.

I have had the opportunity to ask questions about this study and any questions that I have asked have been answered to my satisfaction.

I consent voluntarily to participate as a subject in this study and understand that I have the right to withdraw from this study at any time without in any way affecting my further medical care.

Doctor's signature

Participant's signature

Date

Date

CONSENT FORM FOR PROJECT ENTITLED

"Mifepristone and misoprostol for the termination of pregnancy at 64-140 days since LMP"

(Study code….)

I …… have read/ understood (delete as appropriate) the information about this study that was given / read (delete as appropriate) to me.

I have had the opportunity to ask questions about this study and any question that I have asked have been answered to my satisfaction.

I am also told that I will be provided adequate treatment for any side - effects related to the medications or in case any intervention (like extra hospital stay, surgical termination of pregnancy or evacuation of the uterus) is required. The study centre will bear the cost of treatment. In case any clarification is required, I can contact the staff of……..(name of the clinic) or at telephone number ……..(between ……am. to……. pm) in case of emergency problem.

I consent voluntarily to participate as a subject in this study and understand that I have the right to withdraw from the study at any time and that this will not in any way affect my future medication care.

Name and Signature of witness:

Name and Signature/Thumb Impression of volunteer:

Name and Signature of witness:

Address:

Date:

Place:

Annex C

Flow Chart for Termination of Pregnancy at 10-20 weeks LMP