The Triple M TRIAL

Mifepristone and misoprostol versus misoprostol alone for uterine evacuation after early pregnancy failure: a randomized double blind placebo controlled comparison

Research protocol

(September 2019)

PROTOCOL TITLE 'Mifepristone and misoprostol versus misoprostol alone for uterine evacuation after early pregnancy failure: a randomized double blind placebo controlled comparison (Triple M trial)"

Protocol ID	**Triple M trial**
Short title	**Mifepristone and misoprostol as a treatment for early pregnancy failure**
EudraCT number **ABR – NL number**	**2017-002694-19** **NL 62449.091.17**
Version	**16, september 2019**
Date	**20 september 2019**
Coordinating investigator/project leader	**Prof. dr. F.P.H.A. Vandenbussche** **Radboudumc** **791 Verloskunde & Gynaecologie Stafafdeling** **Postbus 9101, 6500 HB Nijmegen**
Principal investigator(s) (in Dutch: hoofdonderzoeker/uitvoerder) ***Multicenter research: per site***	**Dr. M.P.M.L. Snijders** **Canisius-Wilhelmina Ziekenhuis** **Postbus 9015** **6500 GS Nijmegen** **Drs. E. Hink** **Radboudumc** **791 Verloskunde & Gynaecologie Stafafdeling** **Postbus 9101** **6500 HB Nijmegen** **Dr. R.H.F. van Oppenraaij** **Maasstad Ziekenhuis** **Maasstadweg 21** **3079 DZ Rotterdam** **Dr. W. Hermes** **Haaglanden Medisch Centrum** **Postbus 432** **2501 CK Den Haag** **Dr. P.J.M. van Kesteren** **Onze Lieve Vrouw Gasthuis**

Oosterpark 9
Postbus 95500
1090 HM Amsterdam

Dr. K. De Boer
Rijnstate Ziekenhuis
Wagnerlaan 55
6815 AD Arnhem

Mw. D. Boskamp
VieCuri Medisch Centrum
Tegelseweg 210
5912 BL Venlo

Mw. F.P.J.M. Vrouenraets
Zuyderland Medisch Centrum
Henri Dunantstraat 5
6419 PC Heerlen

Dr. M.M.E. van Rumste
Catharina Ziekenhuis
Michelangelolaan 2
5623 EJ Eindhoven

Dr. G.C.M. Graziosi
St. Antonius Ziekenhuis
Koekoekslaan 1
3435 CM Nieuwegein

Dr. D.P. Van der Ham
Martini Ziekenhuis
Van Swietenplein 1
9728 NT Groningen

Dr. E.C.M. Nelissen
Laurentius Ziekenhuis Roermond
Mgr. Driessenstraat 6
6043 CV Roermond

	Mw. J.A.H. van Seeters **Amphia Ziekenhuis** **Molengracht 21** **4818 CK Breda** **Dr. K.E.A. Hack** **Gelre Ziekenhuizen** **Albert Schweitzerlaan 31** **7334 DZ Apeldoorn** **Dr. A.J.C.M. van Dongen** **Ziekenhuis Gelderse Vallei** **Willy Brandtlaan 10** **6716 RP Ede** **Dr. I.P.M. Gaugler-Senden** **Jeroen Bosch Ziekenhuis** **Henri Dunantstraat 1** **5223 GZ 's-Hertogenbosch** **Dr. L.M. Freeman** **Ikazia Ziekenhuis Rotterdam** **Montessoriweg 1** **3083 AN Rotterdam** **Dr. J.J. Zwart** **Deventer Ziekenhuis** **Nico Bolkesteinlaan 75** **7416 SE Deventer** **Dr. S.F.P.J. Coppus** **Maxima Medisch Centrum** **De Run 4600** **5504 DB Veldhoven** **Drs. C.B.M. Kruijdenberg** **Ziekenhuis St. Jansdal** **Wethouder Jansenlaan 90** **3844 DG Harderwijk**
Sponsor (in Dutch: verrichter/opdrachtgever)	**Universitair Medisch Centrum Radboud**

	Geert Grooteplein 10 **6525 GA Nijmegen NL**
Subsidising party	**Innovatiefonds Zorgverzekeraars** **Postbus 304** **3700 AH Zeist** **Canisius-Wilhelmina Ziekenhuis** **Postbus 9015** **6500 GS Nijmegen**
Independent physician(s)	**Dr. B. Nieboer** **Radboudumc** **791 Verloskunde & Gynaecologie Stafafdeling** **Postbus 9101, 6500 HB Nijmegen**
Pharmacy	**Radboudumc** **864 Apotheek / Clinical Trials Unit** **Postbus 9101, 6500 HB Nijmegen**

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
For non-commercial research, **Head of Department:** **Dhr. J. Wagener** **Radboudumc** **Postbus 9101, 6500 HB Nijmegen**		
Principal Investigator: **Prof. Dr. F.P.H.A. Vandenbussche** **Radboudumc** **791 Verloskunde & Gynaecologie** **Stafafdeling** **Postbus 9101, 6500 HB Nijmegen**		

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)**

SUMMARY

Rationale:
Early pregnancy failure (EPF) is a common complication of pregnancy. Yearly in the Netherlands, 10.000 women with EPF do not abort spontaneously and do receive medical or surgical treatment in order to remove the products of conception from the uterus. For many years, surgical treatment has been the standard treatment. However, medical treatment is a safe and less expensive alternative. Unfortunately, the current medical treatment with misoprostol only has a 54% complete evacuation rate without additional surgery.

Medical treatment for EPF can most probably be improved. For other conditions, such as medical termination of vital pregnancy, the combination of mifepristone with misoprostol has been shown to be superior to the use of misoprostol alone. Based on retrospective data in the Radboud University Medical Centre that are compatible with data from the literature, we expect a complete evacuation rate of at least 67%. However, until now conclusive evidence is lacking.

Objective:
The goal of this study is to test the hypothesis that in early pregnancy failure the sequential combination of mifepristone with misoprostol is superior to the use of misoprostol alone in terms of complete evacuation of the products of conception from the uterus (primary outcome), complications, side effects, costs and patient satisfaction (secondary outcomes).

Study design:
A multi-centred, prospective, two-armed, randomized, double blinded and placebo-controlled trial.

Study population:
Woman with ultrasonography confirmed early pregnancy failure (6-14 weeks postmenstrual), managed expectantly for at least one week.

Intervention:
At day one women allocated to Mifepristone will receive mifepristone 600mg, orally, before starting with the standard treatment.

Control group:
Women allocated to placebo will receive placebo tablets at day one before starting with the standard treatment.

General treatment:
Apart from the study medication, management of participants will be similar in both groups. All women will get two doses of misoprostol 400µg (four hours apart, at day 3 and 4), which will be taken orally at

home.

Main study parameters/endpoints:
Six weeks after treatment, ultrasonography will be performed to determine complete or incomplete evacuation. An endometrial thickness <15mm (maximum anterior-posterior diameter) and no evidence of retained products of conception using only the allocated therapy would be considered as success. The secondary objectives establish patient satisfaction with treatment, side effects, complications and costs.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:
We intend to compare medical treatments that are already applied worldwide for several other indications.
The common undesirable effects mentioned in the information leaflet of mifepristone are nausea, vomiting, diarrhoea, cramping or uterine contractions and bleeding.
Ultrasonography performed after treatment is part of the general treatment.
No additional physical examination is needed for this study, nor will extra blood be taken from the subjects.
Study participants will be asked to fill in standard, validated questionnaires at four different time points.
Participants are followed in an outpatient clinic; hospital admission follows if medically necessary.
According to the risk classification of the NFU for patients participating in this study, the risk has been assessed as "negligible".

1. INTRODUCTION AND RATIONALE

Early pregnancy failure (EPF) is a common complication of pregnancy, as 15% of all pregnancies will end in early pregnancy failure (6-14 weeks). In the Netherlands, there are approximately 15,000 cases per year. [1] The real incidence may be even higher, as not every case is being recognized clinically. [2–4] The incidence of EPF increases with age. Because of rising age in which women tend to have their pregnancies in the Western world, EPF will be of increasing importance.

In the Netherlands, approximately 10,000 women will receive medical or surgical treatment in order to remove the products of conception from the uterus.[1] For many years, surgical treatment (dilatation and curettage, D&C) has been the standard treatment for EPF.[5] However, D&C is associated with risks of complications (0.01-1.16%; pelvic infection, cervical injury, uterine perforation, excessive bleeding, anaesthesia, cervical insufficiency in following pregnancies) and high costs.[6–8]

Medical treatment appears to be a safer and less expensive alternative to surgery. Misoprostol is a synthetic prostaglandin E1 analogue and is currently used in general. Because of an expected spontaneous complete evacuation rate of 50% after expectant management, misoprostol treatment is started generally after a minimum of one week. [5,9] Unfortunately, 46% of the women still have to undergo D&C due to absence of complete evacuation. These numbers are based on retrospective data in the Radboud University Medical Centre (a pilot study) that are compatible with data from the literature.[5,10,11] These women are thus still exposed to the risks of complications associated with surgery.

A new medical treatment option combines mifepristone and misoprostol and seems more effective. Mifepristone is an anti-progesterone and anti-glucocorticoid drug. Administration during pregnancy will increase the production of endogenous prostaglandin by the endometrium, the sensitivity of the gravid uterus to exogenous prostaglandin and the contractility of the myometrium. Mifepristone also causes cervical softening and dilatation.[12,13]

Mifepristone is licensed for four indications including medical termination (of vital pregnancy) up tot 63 days of gestation, termination of pregnancy beyond first trimester, preparation for surgical abortion in the first trimester and labour induction in foetal death in utero in the second and third trimester. The sequential combination of mifepristone with misoprostol has been shown superior to the use of misoprostol alone for medical termination of vital pregnancy and for labour induction in case of foetal death after the first trimester. [14,15] So, it appears reasonable to believe that, also for EPF (non-vital pregnancy in the first trimester), mifepristone with misoprostol will be superior to misoprostol alone.[12] Since the patent on mifepristone has expired, the costs of mifepristone will decrease drastically which makes this treatment option even more attractive.

Several groups have been investigating this new treatment option: the sequential combination of mifepristone with misoprostol. They showed success rates of 66 – 93% without any serious adverse

events.[4,8,11,16–21] All studies concluded that the combination of mifepristone and misoprostol is an effective and safe alternative to surgical treatment. Unfortunately, these data are derived from studies with a number of weaknesses including study design, inclusion criteria, small sample size and medical treatment started directly after the diagnosis without at least one week of expectant management.

A pilot study performed by our research group including women with EPF between 6-14weeks of gestation, showed a success rate of 68,4% (mifepristone + misoprostol) versus 40% (placebo + misoprostol). The need for a second treatment, i.e. surgical intervention, was significantly lower in the mifepristone and misoprostol group as compared to the placebo group: 10,5% versus 50% respectively ($p < 0.05$). However, to prove that in EPF the sequential combination of mifepristone with misoprostol is superior to the use of misoprostol alone, and thus develop an evidence based treatment regimen, a sufficiently powered, randomised, double blinded, and placebo-controlled trial is required.[22]

2. OBJECTIVES

Primary Objective:
Is the sequential combination of mifepristone with misoprostol superior to the use of misoprostol alone in terms of complete evacuation rates in early pregnancy failure?

Primary outcome:

To compare the complete evacuation rate of the products of conception in early pregnancy failure

- sequential mifepristone and misoprostol versus
- sequential placebo and misoprostol

Secondary Objectives:
Establish and compare the rates of

- complications
- side effects
- patient satisfaction
- costs

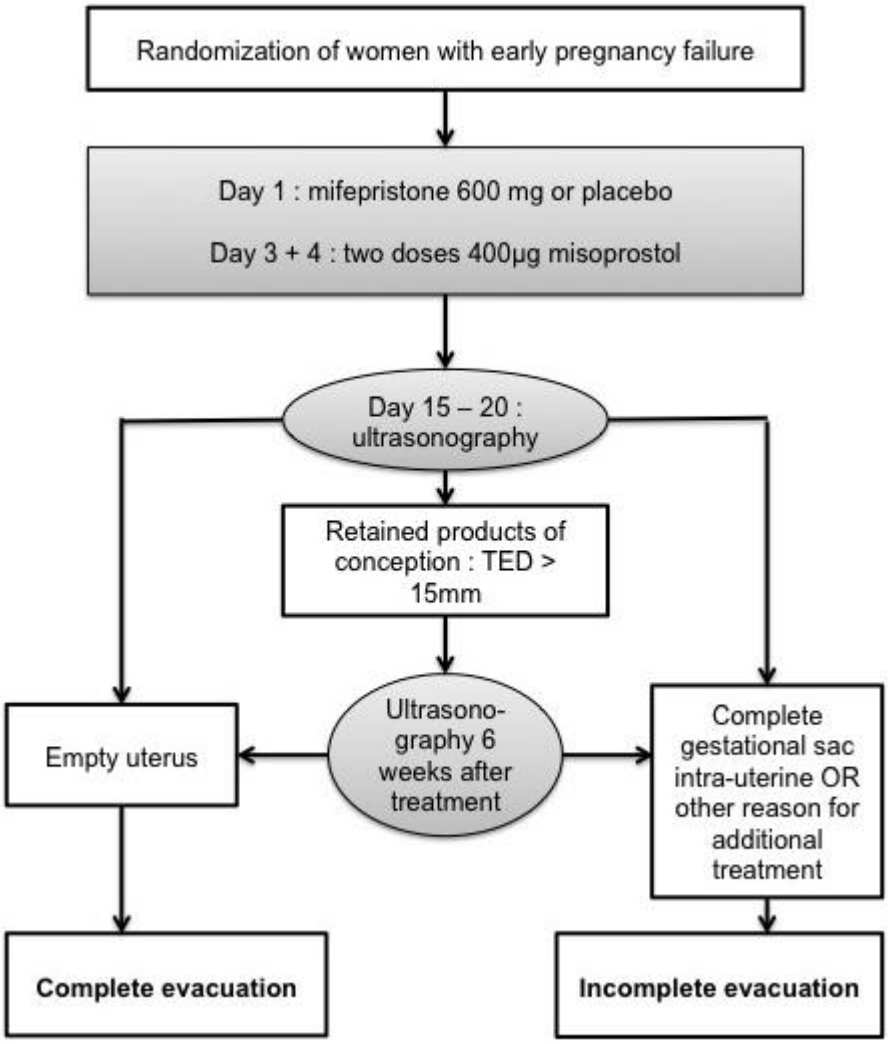
3. STUDY DESIGN

The trial will be performed multi-centred (hospitals) and will be conducted prospectively, two-armed, randomized, double blinded and placebo-controlled. The Clinical Trial Unit of the Radboudumc will coordinate randomisation. Subjects will be randomised in a 1:1 ratio to mifepristone 600mg oral or placebo using computerised randomisation tables. The randomisation will be conducted using block randomisation and stratified by hospital. After randomisation a unique study number will be assigned corresponding with a study package available in the participating centre containing the blinded study medication. The placebo and mifepristone tablets are identical in appearance so neither the patient nor the physician will know which product is taken. Only the pharmacy will know which medication or placebo the patient receives. Blinding, distribution and labelling of the study medication packages will be coordinated by the clinical trial unit in the Radboudumc (Nijmegen). A sealed list with the label codes will be available in case of emergencies. These data will be disclosed to the principal investigators only after data on all outcome parameters have been collected. Regarding misoprostol, the treating physician will prescribe these tablets as usual, which woman can retrieve at their own pharmacy.

Participants are followed in an outpatient clinic; hospital admission follows if medically necessary.

Already seven “STZ-hospitals” showed their interest for participating by signing a letter of intent.

An earlier performed pilot study showed an inclusion-rate of 0.9 patients per week. Based on these numbers, we expect to reach the number of inclusions after eighteen months.


Randomization of women with early pregnancy failure
Day 1 : mifepristone 600 mg or placebo
Day 3 + 4 : two doses 400µg misoprostol
Day 15 – 20 : ultrasonography
Retained products of conception : TED > 15mm
Ultrasono-graphy 6 weeks after treatment
Empty uterus
Complete gestational sac intra-uterine OR other reason for additional treatment
Complete evacuation
Incomplete evacuation

4. STUDY POPULATION

4.1 Population (base)

Woman with a diagnosis of EPF between 6 and 14 weeks of gestation who have been managed expectantly at least one week after the diagnosis has been established. One week of expectant management results in spontaneous complete abortion rates of 50%, and is therefore commonly applied in the Netherlands. EPF is diagnosed using transvaginal ultrasonography. [5,9]

4.2 Inclusion criteria

- Early pregnancy failure, 6-14 weeks postmenstrual
    - Crown-rump length ≥ 6mm and no cardiac activity OR
    - Crown-rump length <6mm and no fetal growth at least one week later OR
    - Gestational sac without embryonic pole
- At least one week after diagnosis OR a discrepancy of at least one week between crown-rump length or gestational sac and calendar gestational age
- Intra-uterine pregnancy
- Women aged above 16 years
- Hemodynamic stable patient (systolic bloodpressure ≥ 90 mmHg, pulse rate ≤ 130/min)
- No signs of infection (increased body temperature, T≥ 38.0°C)
- No signs of incomplete abortion (e.g. vaginal bleeding, substantial abdominal pain)

4.3 Exclusion criteria

- Interaction between study-medication and other medicine
    - Medicinal products and other forms that are CYP3A4 substrates: ketoconazole, itraconazole, erythromycin, rifampicin, dexamethasone, St. John's Wort, certain anticonvulsants (phenytoin, phenobarbital, carbamazepine) and grapefruit juice
    - Magnesium-containing antacids should be avoided during treatment with misoprostol as this may worsen the misoprostol-induced diarrhoea.
- Contraindications for mifepristone or misoprostol
    - chronic adrenal failure
    - hypersensitivity to the active substance or to any of the excipients
    - severe asthma uncontrolled by therapy
    - inherited porphyria
    - pregnancy not confirmed by ultrasound scan or biological tests
    - suspected extra-uterine pregnancy
    - hypersensitivity to misoprostol or to any other prostaglandins

- malnutrition
- renal or liver insufficiency

- Patient does not meet inclusion criteria, discovered after randomization
- Inability to give informed consent
- Language barrier
- Known clotting disorder or use of anticoagulants
- Known risk factors for, or presence of, a cardiovascular disease (e.g. age>35 yrs and smoking, hyperlipidemia, diabetes).

4.4 Sample size calculation

The primary endpoint is classified as complete (success) or incomplete (failure) abortion. We will compare the intervention group (mifepristone and misoprostol) and a control group (placebo and misoprostol).
Based on retrospective data in the Radboud University Medical Center (Nijmegen) that are compatible with data from the literature, we found a complete evacuation rate in the control group in 54% and 67% in the intervention group. We used a success rate of 54% in the control group and 67% in the intervention group for the calculation of the sample size.

An overall significance level of 5%, $\alpha = 0.05$, will be used in combination with a power of 80%, $\beta = 0.20$. A two-sided test will be used. Based on an improvement of complete evacuation rates from 54 tot 67% the trial requires 221 patients in each arm. Considering 3-4% patients lost-to-follow-up, we need to include 230 patients per arm (total 460).

A blinded interim analysis will be done by a data safety monitoring board after including 50% of the required patients in each arm using O'Brien-Fleming stopping rules. This means that if the treatment is particularly beneficial or harmful compared to the control group, the investigators will be able to make a deliberate consideration of terminating the study earlier. The Fisher's exact test will be used to assess the significance of differences between both groups.

Because of the intended execution of an interim analysis, the sample size will have to be adjusted to maintain a sufficient powered final analysis. This leads to a total number of 464 (1.008*460 = 463,68) required inclusions.

5. (NON)-INVESTIGATIONAL MEDICINAL PRODUCT

5.1 Name and description of investigational medicinal product(s)

Mifepristone 600mg, Mifegyne® tablets containing 200mg.

5.2 Name and description of non-investigational medicinal product(s)

Misoprostol 400µg, tablets containing 200µg.

5.3 Summary of findings from non-clinical studies

See appendix SPC (summary of product characteristics) and/or IMPD (Investigational Medicinal Product Dossier).

5.4 Summary of findings from clinical studies

The Royal College of Obstetricians and Gynaecologists (NICE guideline: “The management of early pregnancy loss”) and the “Nederlandse Vereniging voor Obstetrie & Gynaecologie (guideline: “Zwangerschapsafbreking tot 24 weken”) recommend medical methods as a safe, effective and acceptable alternative (evidence level A). Efficacy rates vary widely from 13% to 96% influenced by many factors. Incomplete miscarriage, high-dose of misoprostol and routine ultrasound follow-up were associated with higher success rates. [23,24]

Between 1999 and 2012 five randomized clinical trials are published using mifepristone and misoprostol as a treatment for early pregnancy failure. The randomized controlled trial that addresses our research question in the nearest way, is performed by Stockheim et al, comparing mifepristone and misoprostol versus misoprostol alone. They included 115 patients with EPF until nine weeks of gestation and started treatment immediately. The treatment regimen of the intervention group consisted of mifepristone 600 mg followed by one dose of oral misoprostol 800 µg, and was successful in 65.5%. The control group received no mifepristone but two doses of oral misoprostol 800 µg leading to a complete evacuation rate of 73.6%. There were no serious adverse events. Stockheim et al concluded that mifepristone offers no advantage compared to misoprostol alone because of the high costs of mifepristone. [11]

Three other randomised controlled trials included both women with EPF and incomplete miscarriages. Nielsen et al compared sequential mifepristone and oral misoprostol treatment with expectant management reporting complete evacuation rates of 82% versus 76%. Niinimaki et al compared sequential mifepristone and misoprostol vaginally versus D&C leading to success rates of respectively 90% and 100%. Infections were more common in the D&C group within two months after treatment (2% vs. 15%, p 0.03) and more women with moderate or severe pain were seen in the medical treatment group (63% vs. 37%, p 0.02).[8]

A third study by Torre et al compared immediate versus delayed medical treatment with sequential mifepristone and vaginal misoprostol leading to a statistically significant difference in success rates. Immediate treatment was started directly after diagnosis leading to a complete evacuation rate of 81%. The delayed treatment regimen was started after one week of expectant management. During this week 23% of women experienced a spontaneous complete evacuation, delayed medical treatment was successful in 53% of the remaining women. Since spontaneous abortions during the first week of expectant management in the delayed treatment group were not counted, we concluded that there was no “intention to treat” analysis. Emergency vacuum aspiration was performed in 14% of the woman in the delayed management group versus 5% in the immediate management group. Vacuum aspiration performed on patient request was also recorded as an emergency procedure. The rate of vacuum aspiration in case of retained products of conception was not significantly different between both groups.[21]

In the register for clinical trials (www.clinicaltrials.gov) a randomized, double blinded placebo-controlled trial was uploaded comparing two combinations of drugs in case of EPF, sequential mifepristone with buccal misoprostol versus placebo with buccal misoprostol. Seventeen patients were included; combined mifepristone and misoprostol treatment led to success rates of 62.5% while success rates of 55.6% were described in the placebo group. The trial was prematurely terminated because of poor enrolment. [25]

Other studies describing mifepristone treatment for early pregnancy failure are observational studies or pilot clinical trials. These trials showed success rates of 66 to 93% without any serious adverse events. All concluded that the combination of mifepristone and misoprostol is an effective and safe alternative to surgical treatment. Unfortunately, these data are derived from studies with a number of weaknesses including study design, inclusion criteria, small sample size and medical treatment started directly after the diagnosis without at least one week of expectant management.[16–20]

Luise followed more than 1000 patients with early pregnancy failure for up to four weeks after diagnosis. Successful spontaneous abortion occurred in 52% of women within 14 days of classification. Complication occurred in 1% of expectantly managed patients.[9,26]
Therefore, in the Netherlands, expectant management for at least one week is common practice. Expectant management is a reasonable approach if the woman prefers non-intervention. There are no serious medical risks associated with watchful waiting.[27]

With regards to the follow-up of women receiving medical treatment: ultrasonography seems to be of limited value in predicting the presence of intrauterine remnants shortly after medical treatment. Previous studies do not provide any clear evidence which endometrial thickness corresponds best to the presence of intrauterine pregnancy remnants.[28] A study by Rulin concludes that a maximum anterior-posterior diameter of 15 mm or less, genuine retained products are less likely to be confirmed histologically.[29] Another study by Creinin showed a wide range of endometrial thickness (1-31mm) two

weeks after expulsion of the gestational sac and that endometrial thickness generally decreases with time. No cut-off value appears to be predictive of incomplete abortion in this trial. The authors suggest that clinical signs and symptoms should guide treatment decisions after medical treatment.[30]

5.5 Summary of known and potential risks and benefits

We intend to compare medical treatments that are already applied worldwide for several other indications.
After informed consent and randomization, study participants will take three tablets before starting with the standard treatment, containing either 200mg mifepristone or a placebo. The common undesirable effects mentioned in the information leaflet of mifepristone are nausea, vomiting, diarrhoea, cramping or uterine contractions and bleeding.
Ultrasonography after treatment is part of the standard treatment. No additional physical examination is needed for this study, nor will extra blood be taken from the subjects.
Study participants will receive information and will be asked to fill in standard, validated questionnaires at different time points.
Participants are followed in an outpatient clinic; hospital admission follows if medically necessary.
According to the risk classification of the NFU for patients participating in this study, the risk has been assessed as "negligible".

5.6 Description and justification of route of administration and dosage

The active medication will be 600mg mifepristone. The medication (mifepristone and placebo tablets) is delivered by university hospital pharmacy of the Radboud University Medical Center (Nijmegen). Misoprostol is part of the standard treatment and the participating hospital will provide the tablets.

Mifepristone

A dose of mifepristone 600mg is advised by the manufacturer Exelgyn (Groupe Nordic Pharma) based on phase 2 trials for medical termination of a vital pregnancy up to 63 days gestation. Phase 2 trials showed that 600mg mifepristone was superior to the 200mg dose in terms of complete abortion in case of medical abortion of a vital pregnancy (89% versus 63%).[31,32]

A Cochrane review included one trial comparing low and high doses of mifepristone in case of medical abortion, no significant difference was found regarding the failure rate. There is no difference in side effects compared with lower doses of mifepristone. [12,15,33] There is only one randomized placebo-controlled trial using mifepristone 600mg in case of early pregnancy failure, which showed success rates of 82% (mifepristone) versus 8% (placebo) without any serious adverse events.[22]

Untill now the World Health Organization and the “Nederlandse Vereniging voor Obstetrie en Gynaecologie” advises 200mg mifepristone in case of termination of a vital pregnancy in the first trimester. Due to the high costs of mifepristone, approximately 20 euro for one tablet containing 200mg, and given the context in less-developed countries, the effects were considered as less

relevant. Since the patent on mifepristone has expired, the costs of mifepristone will decrease drastically. To achieve the optimal effect, a dose of 600mg mifepristone will be used in our trial. The effect of mifepristone develops over a time period of 24-48 hours; therefore prostaglandins are usually administered 36-48 hours later.[12,15]

Misoprostol

Misoprostol is part of the standard treatment and will be administered orally because vaginal application may be associated with higher infection rates. Recently, less serious infections have been reported in case of medical abortion after changing the regime of vaginal to buccal administration.[34] There is no difference in success rates. [23,26,35,36] A Cochrane review described a study comparing 800mcg oral with the same dose of vaginal misoprostol with no difference in efficacy, but the mean time to expulsion was significantly longer in the oral group.[4] At the same time several clinical studies comparing oral and vaginal misoprostol have found increased satisfaction with the oral route.[37]

Both groups will receive the current standard treatment 36 – 48 hours after the mifepristone or placebo tablets: two doses of 400mcg misoprostol orally (four hours apart). If no tissue is lost by day 4, two more doses misoprostol 400µg orally (four hours apart) will be taken.[5] A dosage of 800mcg is supported by several studies and is also recommended by the “Nederlandse Vereniging voor Obstetrie en Gynaecologie” in case of medical abortion of a vital pregnancy.[24] A split dosage of misoprostol would be associated with less pain than a protocol using 800µg at one time, and would allow for a longer action in case of a second administration. As there is a balance between mifepristone and misoprostol, adding mifepristone allows for a decrease in misoprostol dosage.

5.7 Dosages, dosage modifications and method of administration of (non)-Investigational Medicinal Product

Patients are offered the choice to take the studymedication under supervision of a healthcare professional or in the privacy of their own house. Multiple studies investigating the safety and efficacy, as well as the acceptability of home us e of mifepristone for medical abortion showed similar safety and efficacy compared to in-clinic adminstration. The most common reason for opting for at home administration was scheduling flexibility, furthermore 96-97,8% of women would recommend home use to a friend, and 97,8-99% would take mifepristone at home again.[38–40] Although in the case of early pregnancy failure there is no termination of a vital pregnancy, it is to be expected that for women in this situation the option to undergo the abortion at home and the scheduling flexibility are equally important.

After informed consent and randomisation, each patient will receive three tablets, containing 200mg mifepristone each or placebo alongside the standard treatment of Misoprostol. Every patient takes home eight tablets, containing 200µg misoprostol each and the studymedication if they opted for home use of Mifepristone..

At day 3 two tablets will be orally swallowed, a second dose of 400µg will be orally swallowed four hours later. In case of tissue loss, no further treatment will be necessary.

In case no tissue is lost by day 4, two more doses of 400µg misoprostol (four hours apart), will be swallowed.
To minimize gastro-intestinal side effects, patients are advised to take the misoprostol tablets right after a meal.

5.8 Preparation and labelling of (non)-Investigational Medicinal Product

The study medication is delivered by university hospital pharmacy of the Radboud University Medical Center (Nijmegen). The pharmacy will label the medication. It will then be delivered to the pharmacies of the participating hospitals; they are responsible for local distribution.
The misoprostol tablets are provided by the participating hospital.

5.9 Drug accountability

The university hospital pharmacy of the Radboud University Medical Center (Nijmegen) will be responsible for the shipment, receipt, disposition, return and destruction of the investigational medicinal products.

6. METHODS

6.1 Study parameters/endpoints

6.1.1 Main study parameter/endpoint

Complete (success) or incomplete (failure) evacuation will be determined six weeks after medical treatment. [5,23,29,30,41–43]

A successful medical treatment will be considered in case of:

- Ultrasonography performed between 15 days and 6 weeks after medical treatment started showing an endometrial thickness <15mm (maximum anterior-posterior diameter) and no evidence of retained products of conception
- using only the allocated therapy,.

6.1.2 Secondary study parameters/endpoints

Ultrasonography will be performed between day 15 and 20 (12 to 17 days after misoprostol treatment) to evaluate endometrial thickness shortly after medical treatment.
Patient satisfaction with treatment will be measured using a standard, validated questionnaire; the Client Satisfaction Questionnaire (CSQ-8) will be filled in six weeks after treatment.
Quality of life will be measured at baseline, one, two and six weeks after treatment started using standard, validated questionnaires such as EuroQOL and Short Form 36.
Patients will receive a registration form to document possible side effects. The treating gynaecologist will document these side effects and complications using the case report form (CRF).

6.2 Randomisation, blinding and treatment allocation

Trained staff will counsel patients, ask informed consent and collect data. Randomization will be coordinated by the university hospital pharmacy in the Radboud University Medical Centre. Subjects will be randomized in a 1:1 ratio to mifepristone 600mg oral or placebo. Randomization will be stratified by centre (to prevent any imbalance between groups in aspects of maternal or neonatal care that may differ between centres) and parity.

After randomization a unique study number will be assigned corresponding with a study package available in the participating center containing the blinded study medication. Blinding, distribution and labeling of the study medication packages will be coordinated by the university hospital pharmacy in the Radboud University Medical Centre (Nijmegen). The study numbers coding mifepristone or placebo are only known in the central pharmacy. These data will be disclosed to the principal investigators only to perform the interim analysis and, if the study continues after the interim analysis, after data on all outcome parameters have been collected. For emergency cases, a closed envelope with the label codes is available at the central pharmacy.

6.3 Study procedures

Early pregnancy failure is diagnosed using transvaginal ultrasonography. The treating gynaecologist will include patients if they meet the inclusion criteria.
After randomization the patient will receive three tablets, each containing a placebo or 200mg mifepristone (day 1).
Then, the standard therapy should be started at day 3. No additional procedures, sampling or laboratory tests are performed. Apart from the study medication, management of participants will be similar in both groups. All women will get two doses of misoprostol 400µg (four hours apart), which will be taken orally at home 36 to 48 hours after the first tablet on day 1. If no tissue is lost by day 4, two more doses of oral misoprostol 400µg (four hours apart) will be taken at home.
To ensure an adequate intake of the study medication patients receive a registration form, to monitor the exact time and dosage of medication they take.

Ultrasonography will be performed between day 15 and 20 to evaluate endometrial thickness shortly after medical treatment. In case of an empty uterus by ultrasonography (TED <15mm), no further evaluation is necessary.
In case of retained products of conception, 3D volumetry and flow measurement of the cavum uteri will be performed, if the assessor is proficient in this procedure. Another ultrasonography will be performed six weeks later, once again including 3D volumetry and flow measurement to determine complete or incomplete evacuation (primary endpoint). During these six weeks, clinical signs and symptoms should guide treatment decisions. In case of clinically stable patients, no additional examination or treatment is necessary until six weeks later.
Examination at the outpatient clinic and additional treatment is a decision made by the treating physician. Additional treatment could be necessary in case of:

- No reaction after treatment (no bleeding or tissue loss)
- Heavy or continuous bleeding
- Persistent abdominal pain
- Fever

If curettage has been performed, no further examinations for the purposes of the study project are necessary.

Anti-D prophylaxis should be given if necessary as part of the standard treatment, following the NVOG-guideline “Erytrocytenimmunisatie en zwangerschap”. Anti-D prophylaxis should be given within 48 hours after evacuation in case of gestational age more than 10 weeks or if curettage has been performed.

At randomisation, during treatment and six weeks after treatment data collected from the clinic maternal charts will be entered into case report form. Primary and secondary outcome measures are subtracted from routine clinical parameters and questionnaires.

6.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Patients who withdraw from the study will remain in their treatment group for the intent-to-treat analysis.

6.5 Follow-up of subjects withdrawn from treatment

As the statistical analysis is planned according to intention to treat principle, patients discontinuing study medication will be analysed in the group that they were originally allocated to.

6.6 Premature termination of the study

A blinded interim analysis will be done by an independent data monitoring board following O'Brien-Fleming stopping rules. This means that if the treatment is particularly beneficial or harmful compared to the control group, the data safety monitoring board will be able to make a deliberate consideration of terminating the study earlier than planned or to reduce the total number of patients.

7. SAFETY REPORTING

7.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

7.2 AEs, SAEs and SUSARs

7.2.1 Adverse and serious adverse events

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / the experimental intervention]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

7.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

The sponsor will report the SAEs through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse events.
An exception to this procedure will be the need for curretage, either at the request of the patient or if medically indicated. Since this is a common procedure in the treatment process of a missed abortion, it will be considered part of the standard care and not an adverse event.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse event. This is for a preliminary report with another 8 days for completion of the report.

7.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:
1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
- Summary of Product Characteristics (SPC) for an authorised medicinal product;
- Investigator's Brochure for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.
The expedited reporting of SUSARs through the web portal ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

7.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, Medicine Evaluation Board and competent authorities of the concerned Member States.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

7.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

7.5 Data Safety Monitoring Board (DSMB)

A DSMB will be established prior to start of the trial. Prior to the start of the trial the DSMB will define criteria to terminate the trial prematurely.

An interim analysis is planned after the follow up data of the first 100 women that have been included is obtained. The interim analysis will be done by a data safety and monitoring board (DSMB) for safety and relevance. As an indication, the trial will be stopped if there is a significant difference in the secondary outcome maternal complications. However, the DSMB is free to make its own judgment. The advice(s) of the DSMB will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

8. STATISTICAL ANALYSIS

Descriptive statistics

The results of the trial will be analysed according to the intention to treat principle.
The effectiveness of the intervention and control treatment will be calculated by relative risks (RR) and 95% confidence intervals.

8.1 Primary study parameter(s)

Data will initially be analysed according the intention to treat method. The main outcome variable, complete evacuation after medical treatment, will be assessed by calculating rates in the two groups, relative risks and 95% confidence intervals as well as numbers needed to treat.
To evaluate the potential of each of the strategies, we will also perform a par protocol analysis, taking into account only those cases that were treated according to protocol.

8.2 Secondary study parameter(s)

Analysis will be performed by intention to treat. Relative risks and 95% confidence intervals will be calculated for the relevant outcome measures.

8.3 Univariate analysis

The Fisher's exact test will be used to assess the significance of differences between both groups (with adapted significance levels according to O'Brien-Fleming).

8.4 Interim analysis

A blinded interim analysis will be done by a data monitoring board following O'Brien-Fleming stopping rules. This means that if the treatment is particularly beneficial or harmful compared to the control group, the Data Safety Monitoring Board (DSMB) will be able to make a deliberate consideration of terminating the study earlier than planned or to reduce the total number of patients.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects Version Edinburgh, Scotland, October 2000, with Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002 end Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

9.2 Recruitment and consent

All patients eligible for this trial will receive information about the study at the outpatient clinic by his/her own practitioner. The patient information letter is provided at the first visit to the hospital. The patients can think about participation in the clinical trial until one week after the diagnosis is made.
On the day of randomization, the treating gynaecologist obtains informed consent.
The research nurse, local investigator or principal investigator is available for further detailed information or questions.

9.3 Objection by minors or incapacitated subjects (if applicable)

These patients are excluded for the current investigation.

9.4 Benefits and risks assessment, group relatedness

We intend to compare medical treatments that are already applied on a large scale in current practice. Study participants will take one extra capsule in comparison with the standard treatment, containing either 600mg mifepristone or a placebo. No additional physical examination is needed for this study, nor will extra blood be taken from the subjects.
Study participants will receive information and fill in standard, validated questionnaires at four different time points.
We do not expect additional risks or benefits.
The common undesirable effects mentioned in the information leaflet of mifepristone are nausea, vomiting, diarrhoea, cramping or uterine contractions and heavy bleeding.

9.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 650.000,-- (i.e. six hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 5.000.000,-- (i.e. five million Euro) for death or injury for all subjects who participate in the Research;
3. € 7.500.000,-- (i.e. seven million five hundred thousand Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10. ADMINISTRATIVE ASPECTS AND PUBLICATION

10.1 Handling and storage of data and documents

Data will be collected using a case report form.
Research nurses and local investigators in each of the participating centres will do data monitoring. Participants will be given a computer generated numeric code. Data handling will be done anonymously, with the patient code only available to the local investigator and the research nurse working in the local centre. A validated data management system will be used for storing all data.

10.2 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.
A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.
Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

10.3 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

10.4 End of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit. In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

10.5 Public disclosure and publication policy

Study results are meant to be published in a scientific journal. Full confidentiality is granted to all study participants, as only completely anonymized data will be presented.

11. STRUCTURED RISK ANALYSIS

11.1 Potential issues of concern

a. Level of knowledge about mechanism of action

As stated in section 1 of this protocol and section 5.1 (pharmacodynamic properties) of the summary of product characteristics of Mifepristone.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

As stated in section 5.3 – 5.4 of this protocol.

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

Not applicable.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

In toxicological studies in rats and monkeys up to a duration of 6 months, mifepristone produced effects related to its antihormonal (antiprogesterone, antiglucocorticoid and antiandrogenic) activity. In reproduction toxicology studies, mifepristone acts as a potent abortifacient. No teratogenic effect of mifepristone was observed in rats and mice surviving foetal exposure. In rabbits surviving foetal exposure, however, isolated cases of severe abnormalities occurred (cranial vault, brain and spinal cord). The number of foetal anomalies was not statistically significant and no dose-effect was observed. In monkeys, the number of fetuses surviving the abortifacient action of mifepristone was insufficient for a conclusive assessment.

e. Analysis of potential effect

As stated in section 5.5 – 5.6.

f. Pharmacokinetic considerations

As stated in section 5.2 (pharmacokinetic properties) of the summary of product characteristics of Mifepristone.

g. Study population

Healthy woman with a diagnosis of EPF between 6 and 14 weeks of gestation who have been managed expectantly at least one week after the diagnosis has been established.

h. Interaction with other products

No interaction studies have been performed. On the basis of this drug's metabolism by CYP3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its

metabolism (increasing serum levels of mifepristone). Furthermore, rifampicin, dexamethasone, St. John's Wort and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum levels of mifepristone).

Based on in vitro inhibition information, co-administration of mifepristone may lead to an increase in serum levels of drugs that are CYP3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP3A4 substrates and have narrow therapeutic range, including some agents used during general anaesthesia.

i. Predictability of effect
Not applicable.

j. Can effects be managed?
No case of overdose has been reported.
In the event of accidental massive ingestion, signs of adrenal failure might occur. Signs of acute intoxication may require specialist treatment including the administration of dexamethasone.

11.2 Synthesis

As stated in section 5.5 Summary of known and potential risks and benefits. We intend to compare medical treatments that are already applied worldwide for several other indications. Explicit in- and exclusion criteria will be maintained. No additional physical examination is needed for this study, nor will extra blood be taken from the subjects.

Participation in this trial has no direct benefits for study participants. Currently, we do not know which medical treatment is superior in case of EPF. The sequential combination of mifepristone with misoprostol may lead to higher success rates; fewer women in the intervention group will be exposed to the risks of a curettage compared to woman in the control group. However, this benefit is not yet proven. If the treatment is particularly beneficial of harmful compared to the control group, the principal investigator will be able to make a deliberate consideration of terminating the study earlier than planned.

According to the risk classification of the NFU for patients participating in this study, the risk has been assessed as "negligible".

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