ISRCTN17405024 https://doi.org/10.1186/ISRCTN17405024

A trial to test if using a combination of drugs (mifepristone followed by misoprostol) is better than giving misoprostol alone to more quickly resolve a miscarriage

Submission date
27/02/2017

Recruitment status
No longer recruiting

Registration date
01/03/2017

Overall study status
Completed

Last Edited
11/08/2022

Condition category
Pregnancy and Childbirth

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
Miscarriage is where a woman loses the baby she is carrying. It is the most common complication of pregnancy, affecting 15-25% of pregnancies bringing the total in England to approximately 125,000 per year. Miscarriage often brings not only physical pain, bleeding and risks of infection, but also emotional issues on women and their families. A missed miscarriage, also known as a missed abortion or a silent miscarriage, occurs when the baby dies, but the body does not recognise this and so the pregnancy sac (where the baby grows) stays inside the body. Women who have had a missed miscarriage often opt for medical management up to 13+6 weeks of pregnancy. NICE currently recommends that a drug called misoprostol (a vaginal pessary (medication inserted into the vagina) or tablet that makes the womb contract) should be used in the medical treatment of miscarriage. However, there is evidence to suggest that combining this drug with mifepristone (an oral tablet that reduces pregnancy hormones) may be more effective in treating miscarriage. The aim of this study is to find out whether treating women with mifepristone followed by misoprostol, is more effective than misoprostol alone at resolving missed miscarriage.

Who can participate?
Women aged 16 years and over who have been diagnosed with a missed miscarriage

What does the study involve?
Participants are randomly allocated to one of two groups. Those in the first group receive mifepristone followed by misoprostol and those in the second group receive a dummy drug (placebo) followed by misoprostol. Neither the participants nor the researchers know which women receive which drug. Women in both groups are then monitored for 7 days to find out how many miscarriages are resolved (complete) in each group. If miscarriage is not complete then further treatment (more tablets or surgery) is offered.

What are the possible benefits and risks of participating?
It is not known whether women will benefit personally from taking part in this study, but the knowledge gained thanks to their help will inform future treatment and potentially lead to improved treatment of miscarriage for women in the future. Mifepristone blocks the action of the hormone progesterone to help speed up the process of miscarriage. As a consequence, patients may experience increased vaginal bleeding. All patients who take part will receive misoprostol, which helps the uterus contract to push out the pregnancy tissue and can cause period-like cramps, sickness, diarrhoea and flu-like symptoms. If patients have any concerns, they are advised to contact the research nurse/midwife at their hospital. Patients will be provided with a card to carry and give to anyone treating them, informing them that they are taking part in this study.

Where is the study run from?
1. Birmingham Women's Hospital (UK)
2. Queen Alexandra Hospital, Portsmouth (UK)
3. Queen's Medical Centre, Nottingham (UK)
4. Sunderland Royal Hospital (UK)
5. University Hospital Coventry (UK)
6. Royal London Hospital (UK)
7. Whipps Cross Hospital (UK)
8. Newham University Hospital (UK)
9. Birmingham Heartlands Hospital (UK)
10. Glasgow Royal Infirmary (UK)
11. Queen Elizabeth University Hospital, Glasgow (UK)
12. King's College Hospital (UK)
13. Liverpool Women's Hospital (UK)
14. Princess Anne Hospital, Southampton (UK)
15. Royal Infirmary of Edinburgh (UK)
16. Royal Victoria Infirmary, Newcastle (UK)
17. St Thomas' Hospital (UK)
18. St Michael's University Hospital, Bristol (UK)
19. University College Hospital, London (UK)
20. Epsom Hospital (UK)
21. Southmead Hospital (UK)
22. West Middlesex Hospital (UK)
23. Chelsea and Westminster Hospital (UK)
24. Princess Royal Hospital (UK)
25. Singleton Hospital (UK)
26. Princess of Wales Hospital (UK)
27. Burnley General Hospital (UK)
28. St Helier Hospital (UK)

When is the study starting and how long is it expected to run for?
February 2017 to July 2020 (updated 31/03/2020, previously: January 2020)

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
Mrs Leanne Beeson
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Contact information

Type(s)
Public

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT03065660

Clinical Trials Information System (CTIS)
2016-005097-35

Protocol serial number
RG_16-076

Study information

Scientific Title
A randomised placebo-controlled trial of mifepristone and misoprostol versus misoprostol alone in the medical management of missed miscarriage

Acronym
MifeMiso

Study objectives
Current study hypothesis as of 10/05/2018:
Treatment with mifepristone plus misoprostol is superior to misoprostol alone for the resolution of miscarriage within 7 days in women diagnosed with missed miscarriage by pelvic ultrasound scan in the first 13+6 weeks of pregnancy.

Previous study hypothesis:
Treatment with mifepristone plus misoprostol is superior to misoprostol alone for the resolution of miscarriage within 7 days by at least 10% in women diagnosed with missed miscarriage by pelvic ultrasound scan in the first 13+6 weeks of pregnancy.

Ethics approval required
Old ethics approval format

Ethics approval(s)
14/02/2017, ref: 17/WM/0017

Primary study design
Interventional

Study design
Randomised; Interventional; Design type: Treatment, Drug

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Miscarriage

Interventions
Current interventions as of 10/05/2018:
Participants will be randomised on-line via a secure internet facility in a 1:1 ratio through a third party independent Integrated Trial Management System (MedSciNet Clinical Trial Framework). A “minimisation” procedure using a computer-based algorithm will be used to avoid chance imbalances in the following important variables: Maternal age (<30, ≥30 years), body mass index (<35, ≥35 kg/m2), previous parity (nulliparous, parous women), gestational age (<70, ≥70 days), amount of bleeding (PBAC score; ≤2, ≥3) and randomising centre.
710 women in total will be randomised; 355 participants each in the mifepristone and placebo arms.
Participants in the mifepristone arm will receive a single dose of oral mifepristone 200 mg, followed by a single dose of vaginal, oral or sublingual misoprostol 800 mcg 2 days later.
Participants in the placebo arm will receive a single oral placebo tablet followed by a single dose of vaginal, oral or sublingual misoprostol 800 mcg 2 days later
All women will be clinically followed up until they are discharged upon confirmation of a negative pregnancy test result and resolution of the miscarriage. Upon discharge all women will be requested to complete a follow up EQ-5D-5L questionnaire and Qualitative Patient Satisfaction Questionnaire which should be returned as soon as possible following discharge. A subset of women will be selected for an in depth interview to discuss the treatment they received up to 6 weeks after discharge based on their responses to the Qualitative Patient Satisfaction Questionnaire.

Previous interventions:
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Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Mifepristone

Primary outcome(s)
Current primary outcome measure as of 09/08/2019:
Failure to spontaneously pass the gestational sac within 7 days after randomisation is assessed within 7 days after randomisation by pelvic ultrasound scan (where possible)

Previous primary outcome measure from 10/05/2018 to 09/08/2019:
Failure to spontaneously pass the gestational sac within 7 days after randomisation is assessed within 7 days after randomisation by pelvic ultrasound scan

Original primary outcome measure:
Failure to spontaneously pass gestational sac within 7 days after start of the medical treatment is assessed within 7 days after start of medical treatment by pelvic ultrasound scan.

Key secondary outcome(s)
Current secondary outcome measures as of 09/08/2019:
Key Secondary Outcome:
Surgical intervention to resolve the miscarriage (collected up to discharge from EPU care) is assessed from randomisation until discharge up to approximately 8 weeks by clinical review (surgical intervention information recorded on the Outcomes CRF)

Other Secondary Outcomes:
1. Surgical intervention to resolve the miscarriage up to and including day 7 post-randomisation is assessed from randomisation until day 7 post-randomisation by clinical review (surgical intervention information recorded on the Outcomes CRF)
2. Surgical intervention to resolve the miscarriage after day 7 post-randomisation to discharge from EPU care is assessed from day 8 post-randomisation until discharge up to approximately 8

weeks by clinical review (surgical intervention information recorded on the Outcomes CRF)
3. Need for further doses of misoprostol up to day 7 post-randomisation is assessed after initial 800 mcg dose of misoprostol at day 2 until day 7 post-randomisation (information collected on Outcomes case report form [CRF])
4. Need for further doses of misoprostol up to discharge from EPU care is assessed after initial 800 mcg dose of misoprostol at day 2 until discharge by clinical review (information collected on Outcomes case report form [CRF])
5. Overall patient satisfaction score is assessed within 6 weeks of discharge from EPU care using the CSQ-8 Client Satisfaction Questionnaire
6. Patient quality of life (Index value and overall health status) is assessed using the EQ-5D-5L questionnaire and collected on date of randomisation, day 6-7 post-randomisation or day of follow-up USS if different to day 6-7 and day 21 +/- 2 days post-randomisation. If a woman obtains an initial positive pregnancy test result at day 21 +/- 2 days post-randomisation then a further EQ-5D-5L questionnaire is collected upon discharge from EPU care)
7. Duration of bleeding reported by woman (days) is assessed from randomisation until discharge from EPU care, up to approximately 8 weeks by the patient self-reporting (information recorded on the Outcomes CRF)
8. Diagnosis of infection associated with miscarriage requiring outpatient antibiotic treatment is assessed from randomisation until discharge from EPU care, up to approximately 8 weeks by clinical review (information recorded on the Outcomes CRF)
9. Diagnosis of infection associated with miscarriage requiring inpatient antibiotic treatment is assessed from randomisation until discharge from EPU care, up to approximately 8 weeks by clinical review (information recorded on the Outcomes CRF)
10. Negative pregnancy test result 21 days (+/- 2 days) after randomisation is assessed 21 days (+/- 2 days) after randomisation by patient performed pregnancy test (information recorded on the Outcomes CRF)
11. Time from randomisation to discharge from EPU care (described using summary statistics only) is measured in days, assessed up to approximately 8 weeks by calculating the days between randomisation (recorded on the Randomisation form) and discharge from EPU care (recorded on the Outcomes CRF)
12. Outpatient or emergency visits are recorded from randomisation until discharge from EPU care, up to approximately 8 weeks by reviewing patient notes (recorded on the Outcomes CRF)
13. Inpatient admissions (nights in hospital) are assessed from randomisation until discharge from EPU care, up to approximately 8 weeks by reviewing patient notes (recorded on the Outcomes CRF)

Safety Outcomes:
1. Blood transfusion required is assessed from randomisation until discharge from EPU care, up to approximately 8 weeks by clinical review (information recorded on the Outcomes CRF)
2. Side effects are measured from randomisation until discharge from EPU care, assessed up to approximately 8 weeks by clinical review and/or patient self-reporting (adverse events and serious adverse events recorded on respective forms)
3. Death is assessed from randomisation until discharge from EPU care, up to approximately 8 weeks by clinical review (recorded on SAE form)
4. Any serious complications is assessed from randomisation until discharge from EPU care, up to approximately 8 weeks by clinical review (recorded on SAE form)

Previous secondary outcome measured from 10/05/2018 to 09/08/2019:
1. Need for further doses of misoprostol up to day 7 post-randomisation is assessed after initial 800 mcg dose of misoprostol at day 2 until day 7 post-randomisation (information collected on Outcomes case report form [CRF])
2. Need for further doses of misoprostol up to discharge from EPU care is assessed after initial

800 mcg dose of misoprostol at day 2 until discharge by clinical review (information collected on Outcomes case report form [CRF])
3. Time from randomisation to passage of gestational sac is assessed up to approximately 8 weeks by calculating the days between randomisation (recorded on the Randomisation form) and passage of the gestational sac (recorded on the Outcomes CRF)
4. Time from active treatment (defined as mifepristone in the active group and misoprostol in the placebo group) commencement to passage of gestational sac is assessed up to approximately 8 weeks by calculating the days between active treatment commencement (mifepristone/misoprostol; recorded on the Outcomes CRF) and passage of the gestational sac (also recorded on the Outcomes CRF)
5. Surgical intervention to resolve the miscarriage (collected up to discharge from EPU care) is assessed from randomisation until discharge up to approximately 8 weeks by clinical review (surgical intervention information recorded on the Outcomes CRF)
6. Overall patient satisfaction score is assessed within 6 weeks of discharge from EPU care using the CSQ-8 Client Satisfaction Questionnaire
7. Patient quality of life (Index value and overall health status) is assessed using the EQ-5D-5L questionnaire and collected on date of randomisation, day 6-7 post-randomisation or day of follow-up USS if different to day 6-7 and day 21 +/- 2 days post-randomisation. If a woman obtains an initial positive pregnancy test result at day 21 +/- 2 days post-randomisation then a further EQ-5D-5L questionnaire is collected upon discharge from EPU care)
8. Blood transfusion required is assessed from randomisation until discharge from EPU care, up to approximately 8 weeks by clinical review (information recorded on the Outcomes CRF)
9. Duration of bleeding reported by woman (days) is assessed from randomisation until discharge from EPU care, up to approximately 8 weeks by the patient self-reporting (information recorded on the Outcomes CRF)
10. Diagnosis of infection associated with miscarriage requiring outpatient antibiotic treatment is assessed from randomisation until discharge from EPU care, up to approximately 8 weeks by clinical review (information recorded on the Outcomes CRF)
11. Diagnosis of infection associated with miscarriage requiring inpatient antibiotic treatment is assessed from randomisation until discharge from EPU care, up to approximately 8 weeks by clinical review (information recorded on the Outcomes CRF)
12. Negative pregnancy test result 21 days (+/- 2 days) after randomisation is assessed 21 days (+/- 2 days) after randomisation by patient performed pregnancy test (information recorded on the Outcomes CRF)
13. Time from randomisation to discharge from EPU care is measured in days, assessed up to approximately 8 weeks by calculating the days between randomisation (recorded on the Randomisation form) and discharge from EPU care (recorded on the Outcomes CRF)
14. Side effects are measured from randomisation until discharge from EPU care, assessed up to approximately 8 weeks by clinical review and/or patient self-reporting (adverse events and serious adverse events recorded on respective forms
15. Death is assessed from randomisation until discharge from EPU care, up to approximately 8 weeks by clinical review (recorded on SAE form)
16. Any serious complications is assessed from randomisation until discharge from EPU care, up to approximately 8 weeks by clinical review (recorded on SAE form)
17. Outpatient or emergency visits are recorded from randomisation until discharge from EPU care, up to approximately 8 weeks by reviewing patient notes (recorded on the Outcomes CRF)
18. Inpatient admissions (nights in hospital) are assessed from randomisation until discharge from EPU care, up to approximately 8 weeks by reviewing patient notes (recorded on the Outcomes CRF)

Original secondary outcome measures:
1. Need for further doses of misoprostol is assessed after initial 800mcg dose of misoprostol at

day 2 until discharge by clinical review (information collected on Outcomes case report form [CRF])
2. Time from randomisation to passage of gestational sac is assessed up to 8 weeks by calculating the days between randomisation (recorded on the Randomisation form) and passage of the gestational sac (recorded on the Outcomes CRF)
3. Time from active treatment commencement to passage of gestational sac is assessed up to 8 weeks by calculating the days between active treatment commencement (mifepristone /misoprostol; recorded on the Outcomes CRF) and passage of the gestational sac (also recorded on the Outcomes CRF)
4. Expulsion of the gestational sac without the need for surgery is assessed from randomisation until discharge up to 8 weeks by clinical review (surgical intervention information recorded on the Outcomes CRF)
5. Unplanned surgery is assessed from randomisation until discharge, up to 8 weeks by clinical review (surgical intervention information recorded on the Outcomes CRF)
6. Patient satisfaction is assessed within 6 weeks of discharge using the CSQ-8 Client Satisfaction Questionnaire
7. Patient quality of life is assessed at baseline, 6-7 days after start of medical treatment and upon discharge using the EQ-5D-5L questionnaire
8. Blood transfusion rate is assessed from randomisation until discharge, up to 8 weeks by clinical review (information recorded on the Outcomes CRF)
9. Days of bleeding is assessed from randomisation until discharge, up to 8 weeks by the patient self-reporting (information recorded on the Outcomes CRF)
10. Infection requiring outpatient antibiotics treatment is assessed from randomisation until discharge, up to 8 weeks by clinical review (information recorded on the Outcomes CRF)
11. Infection requiring inpatient treatment rate is assessed from randomisation until discharge, up to 8 weeks by clinical review (information recorded on the Outcomes CRF)
12. Negative pregnancy test result is assessed 21 days after start of medical treatment by patient performed pregnancy test (information recorded on the Outcomes CRF)
13. Time from start of medical treatment to discharge is measured in days, assessed up to 8 weeks by calculating the days between start of medical treatment (mifepristone/placebo; recorded on the Outcomes CRF) and passage of the gestational sac (recorded on the Outcomes CRF)
14. Side effects are measured from randomisation until discharge, assessed up to 8 weeks by clinical review and/or patient self-reporting (adverse events and serious adverse events recorded on respective forms)
15. Death or serious complication rate is assessed from randomisation until discharge, up to 8 weeks by clinical review (death information recorded on SAE form)
16. Outpatient or emergency visits are recorded from randomisation until discharge, up to 8 weeks by reviewing patient notes (recorded on the Outcomes CRF)
17. Inpatient admissions (nights in hospital) are assessed from randomisation until discharge, up to 8 weeks by reviewing patient notes (recorded on the Outcomes CRF)

Completion date
31/07/2020

Eligibility

Key inclusion criteria

1. Women diagnosed with missed miscarriage by pelvic ultrasound scan in the first 13+6 weeks of pregnancy
2. Age 16 years and over
3. Willing and able to give informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
16 Years

Sex
Female

Total final enrolment
711

Key exclusion criteria
Current participant exclusion criteria as of 10/05/2018:
1. Women opting for alternative methods of miscarriage management (expectant or surgical)
2. Diagnosis of incomplete miscarriage
3. Life-threatening bleeding
4. Contraindications to mifepristone or misoprostol use for example chronic adrenal failure, known hypersensitivity to either drug, haemorrhagic disorders and anticoagulant therapy, prosthetic heart valve or history of endocarditis, existing cardiovascular disease, severe asthma uncontrolled by therapy or inherited porphyria
5. Participation in any other blinded, placebo-controlled trials of investigational medicinal products in pregnancy
6. Previous participation in the MifeMiso trial
7. Woman not able to attend for day 6-7 ultrasound scan

Previous participant exclusion criteria:
1. Women opting for alternative methods of miscarriage management (expectant or surgical)
2. Diagnosis of incomplete miscarriage
3. Life threatening bleeding
4. Contraindications to mifepristone or misoprostol use including chronic adrenal failure, known hypersensitivity to either drug, haemorrhagic disorders and anticoagulant therapy, prosthetic heart valve or history of endocarditis, existing cardiovascular disease, severe asthma uncontrolled by therapy or inherited porphyria
5. Participation in any other blinded, placebo-controlled trials of investigational medicinal products in pregnancy

Date of first enrolment
20/09/2017

Date of final enrolment
31/07/2019

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
Birmingham Women's Hospital
Mindelsohn Way
Birmingham
United Kingdom
B15 2TG

Study participating centre
Queen Alexandra Hospital
Portsmouth
United Kingdom
PO6 3LY

Study participating centre
Queen's Medical Centre
Nottingham
United Kingdom
NG7 2UH

Study participating centre
Sunderland Royal Hospital
Sunderland
United Kingdom
SR4 7TP

Study participating centre

University Hospital Coventry
Coventry
United Kingdom
CV2 2DX

Study participating centre
Royal London Hospital
London
United Kingdom
E1 1BB

Study participating centre
Whipps Cross Hospital
London
United Kingdom
E11 1NR

Study participating centre
Newham University Hospital
London
United Kingdom
E13 8SL

Study participating centre
Birmingham Heartlands Hospital
Birmingham
United Kingdom
B9 5SS

Study participating centre
Glasgow Royal Infirmary
Glasgow
United Kingdom
G4 0SF

Study participating centre

Queen Elizabeth University Hospital
Glasgow
United Kingdom
G51 4TF

Study participating centre
King's College Hospital
London
United Kingdom
SE5 9RS

Study participating centre
Liverpool Women's Hospital
Liverpool
United Kingdom
L8 7SS

Study participating centre
Princess Anne Hospital
Southampton
United Kingdom
SO16 5YA

Study participating centre
Royal Infirmary of Edinburgh
Edinburgh
United Kingdom
EH16 4SA

Study participating centre
Royal Victoria Infirmary
Newcastle
United Kingdom
NE1 4LP

Study participating centre

St Thomas' Hospital
London
United Kingdom
SE1 7EH

Study participating centre
St Michael's University Hospital
Bristol
United Kingdom
BS2 8EG

Study participating centre
University College Hospital
London
United Kingdom
NW1 2BU

Study participating centre
Birmingham Women's Hospital
Mindelsohn Way
Birmingham
United Kingdom
B15 2TG

Study participating centre
Epsom Hospital
Dorking Road
Epsom
United Kingdom
KT18 7EG

Study participating centre
Southmead Hospital
Southmead Road
Westbury-on-Trym
Bristol
United Kingdom
BS10 5NB

Study participating centre
West Middlesex Hospital
Twickenham Road
Isleworth
United Kingdom
TW7 6AF

Study participating centre
Chelsea and Westminster Hospital
369 Fulham Road
Chelsea
London
United Kingdom
SW10 9NH

Study participating centre
Princess Royal Hospital
Apley Castle
Apley
Telford
United Kingdom
TF1 6TF

Study participating centre
Singleton Hospital
Sketty Lane
Sketty
Swansea
United Kingdom
SA2 8QA

Study participating centre
Princess of Wales Hospital
Coity Road
Bridgend
United Kingdom
CF31 1RQ

Study participating centre
Burnley General Hospital
Casterton Avenue

Burnley
United Kingdom
BB10 2PQ

Study participating centre
St Helier Hospital
Wrythe Lane
Carshalton
United Kingdom
SM5 1AA

Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study may be available upon request from a.coomarasamy@bham.ac.uk

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/09/2020	27/08/2020	Yes	No
Results article	cost-effectiveness results	01/08/2021	01/06/2021	Yes	No
Results article	results	01/11/2021	26/11/2021	Yes	No
HRA research summary			28/06/2023	No	No
Protocol file	version 5.0	27/06/2019	11/08/2022	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes