Academic and Clinical Central Office for Research and Development

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Study Protocol

An open label exploratory study to assess the safety of using 100mg of methotrexate as a standard dose treatment for women with unruptured ectopic pregnancy

OSPREY

Co-sponsors	The University of Edinburgh & Lothian Health Board ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
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Lothian

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PROTOCOL APPROVAL SIGNATURE PAGE

An open label exploratory study to assess the safety of using 100mg of methotrexate as a standard dose treatment for women with unruptured ectopic pregnancy

OSPREY

EudraCT 2020-004592-40

The undersigned accept the content of this protocol in accordance with the appropriate regulations and agree to adhere to it throughout the execution of the study.

Andrew Horne			
Chief Investigator	**Signature**	**Date**	
Colin Duncan			
Trial Statistician	**Signature**	**Date**	
Neil Mitchell			
Lead Co-Sponsor Representative	**Signature**	**Date**	

The Principal Investigator must sign below to document that the protocol has been read and understood.

Principal Investigator	**Signature**	**Site**	**Date**

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LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CSR	Clinical Study Report
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EP	Ectopic Pregnancy
EudraCT	European Clinical Trials Database
FBC	Full Blood Count
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
LFT	Liver Function Tests
MHRA	Medicines and Healthcare products Regulatory Agency
MTX	Methotrexate
PI	Principal Investigator
NIMP	Non-Investigational Medicinal Product

QA	Quality Assurance
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
U&E	Urea and Electrolytes

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TRIAL SUMMARY

Trial Title	An open label exploratory study to assess the safety of using 100mg of methotrexate as a standard dose treatment for women with unruptured ectopic pregnancy
Study Acronym	OSPREY
Clinical Phase	Therapeutic use trial (Phase IV)
Trial Design	Single site open label exploratory study
Trial Participants	Women with a stable EP who have consented to medical treatment with MTX
Planned Number of Participants	Ten
Planned Number of Sites	One
Countries Anticipated to be Involved in Trial	Scotland
Treatment Duration	Single injection
Follow up Duration	No long term follow up
Total Planned Trial Duration	One year
Primary Objective	To explore the safety of 100 mg/ml dose of MTX in patients who routinely would receive 85 mg or lower based on their body surface area.
Secondary Objectives	To compare outcomes of the 100 mg/ml dose of MTX in patients who routinely would receive 85 mg or lower based on their body surface area.
Primary Endpoint	- Adverse events - Haematological, renal and liver function.
Secondary Endpoint	- Time to resolution of EP (number of days from first MTX administration until resolution of EP) - Treatment failure (requirement for second injection with MTX or requirement for surgical intervention)
IMP(s)	Methotrexate (MTX)
IMP Route of Administration	Single intra muscular injection
NIMP(s)	N/A

Lay Summary of Trial	We will explore the feasibility of giving women who have a stable, ectopic pregnancy (a pregnancy that has implanted in the Fallopian tube and not the uterus) a single dose of methotrexate of 100mg/ml. Methotrexate is a drug used to treat ectopic pregnancies and is usual standard care when a patient presents in a stable condition. The dose is calculated depending on the patient's body surface area (calculated using height and weight). The differing doses then have to be prepared in pharmacies (these range between 60mgs and 120mg). This adds to waiting times and burden on patients. The aim of this study is to find out whether we can safely give all women a standard dose. We will recruit women who have a stable ectopic pregnancy and give then a standard one-off dose of methotrexate of 100mg/ml. All of the women recruited to the study would normally have received less than 100mgs of methotrexate had they received standard care. We will follow them up as per usual clinical care (no extra visits) until the pregnancy resolves. We will look at side effects experienced by these women and compare these to side effects experienced by the women who are given a slightly lower dose (published historical data).

1. INTRODUCTION

1.1 BACKGROUND

Tubal ectopic pregnancy (EP) occurs when an embryo implants in the Fallopian tube rather than the uterus. As the pregnancy grows, it causes stretching and ultimately rupture of the tube, causing life-threatening internal bleeding. The incidence of EP is 1-2% of all pregnancies and it is a leading cause of maternal morbidity and mortality in the first trimester.

Options for management of unruptured tubal EP are surgical removal of the embryo (salpingostomy) or the Fallopian tube with the pregnancy (salpingectomy), medical treatment with methotrexate (MTX) to terminate the embryo in situ or conservative management. The medical management of EP has not changed since the late 1980s when this practice was first introduced.

1.2 RATIONALE FOR STUDY

There are three most often used MTX protocols: the treatment can be administered via intramuscular injection as a single dose, two doses or multiple doses at 50 mg/m^2 or 1 mg/kg. These treatment regimens used in current clinical practice are derived from publications from the late 1980s and have not changed since then, although refinement of the target population most suited for treatment with MTX has occurred. Although no MTX formulation is approved for the management of EP, it is an established approach and included in clinical guidance from the Royal College of Obstetricians and Gynaecologists (1) and the National Institute of Clinical Excellence (2). There is no pharmacological data to provide evidence as to which dosing regime is most effective and safest for patients. Meta-analysis of MTX use in the treatment of EP demonstrates that the single-dose protocol carries a higher risk of failed treatment but is associated with fewer side effects than the multi-dose protocol (3), therefore this has been adopted as the best risk to benefit treatment. Indeed UK guidelines, recommend a single treatment (50 mg/m^2 body surface) which is only repeated if levels of hCG are not seen to fall in the subsequent days.

Clinical practice across Europe varies with regards to the protocol, dosing regime and preparation of MTX in pharmacies. For example, the drug can be purchased in pre-filled syringes of different volumes at a low concentration of 25 mg/ml, or can be prepared from glass vials at concentration of 25 mg/ml or 100 mg/ml on per patient basis. In the UK it is standard practice to use pre-filled syringes at 25 mg/ml to make up the final dose with banding calculations in 5 mg increments. This means that patients will receive a dose from 70 mg to a maximum of 100 mg based on body surface area. There is little evidence for the use of a 100 mg, which is well-tolerated, ceiling but a suggestion that the efficacy doesn't improve with higher doses in obese women with a body surface area >2m^2, potentially because of administration difficulties in women with increased subcutaneous adiposity. The modal dose of MTX in Edinburgh is 85 mg. The requirement for dose calculation and dose preparation carry a risk of errors as well as an extended waiting time for patients to receive treatment. The standardisation of MTX to a single dose would have benefits to patients in regards to waiting times and benefits to the NHS with regards to negating potential for error and waiting time for treatment.

We propose to investigate the safety of a standardised 100 mg dose of MTX in treatment of EP in women who would routinely receive a dose of 85 mg or lower based on their body surface area (i.e. the dose will be higher than 50 mg/m^2). This will not impede the efficacy of the treatment compared to standard clinical practice, and could potentially reduce the need for a second MTX injection (around 15% of cases) or rescue surgery (around 15% of cases) and the inherent risks of surgical complications. The safety profile will be assessed by recording side effects and adverse events and these will be compared to the safety profile observed in historical data of patients who received the routine dose of 50 mg/m^2. We will

compare this will clinical data that has been collected during a clinical audit of side effects and efficacy (.Methotrexate and the Medical Management of Ectopic Pregnancy: Clinical and Subclinical Side Effects, Alexandria Haines, Reproductive Biology Honours Project 2019-2020.This data is anonymised.
The study will provide preliminary data on the safety profile of a standardised, ready to use 100mg dose of MTX which is currently used off license for treatment EP, the results of this study will be used to support formal clinical development. This will also inform the design of a large randomised clinical trial to further investigate safety, efficacy and acceptability of using a standardised ready to use dose of MTX.

2. STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

To explore the safety of 100 mg/ml dose of MTX in patients who routinely would receive 85 mg or lower based on their body surface area.

2.1.2 Secondary Objectives

To compare outcomes of the 100 mg/ml dose of MTX in patients who routinely would receive 85 mg or lower based on their body surface area.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

- Adverse events
- Haematological, renal and liver function (results from FBC, U&Es and LFTs).

2.2.2 Secondary Endpoints

- Time to resolution of EP (number of days from first MTX administration until resolution of EP)
- Treatment failure (requirement for second injection with MTX or requirement for surgical intervention)

3. STUDY DESIGN

Osprey is a single site open label exploratory study of the safety and outcomes of using a pre-prepared single dose of 100 mg/ml MTX in women with a stable EP. Recruitment is anticipated to occur over a period of 6 months and the entire trial will run for 12 months. Participants will be recruited from early pregnancy unit, gynaecology outpatient department and inpatient wards at the Royal Infirmary of Edinburgh. They will receive a single intramuscular injection of MTX at 100 mg/ml dose. At present this would be given in a 4ml injection and we propose this will be given in a 1ml, ready-to-use injection. The patients will be required to come to the hospital for follow up visits as part of their standard clinical care to monitor serum hCG levels until it falls to non-pregnant levels (≤15IU/l) and the EP can be declared as resolved or it is determined surgical management is warranted. In order to assess safety of the increased dose, the patients will have blood tests (hCG,

LFT, U&E and FBC) carried out usually at day 4, 7 and then weekly after the treatments with MTX and will be contacted to ask about side effects and adverse events. LFT, U&E and FBC will only be taken after day 7 if clinically required. We will take blood samples during scheduled clinical care visits to reduce number of visits.

4. STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

We will recruit 10 women with a stable, EP who have consented to medical treatment with MTX. The recruitment will take place at Royal Infirmary of Edinburgh. We will recruit over 6 months and all consented women will receive a single intramuscular injection of MTX at the 100mg dose.

4.2 INCLUSION CRITERIA

- Clinical decision made for treatment with MTX
- Women aged between 18-45
- Serum hCG>15 IU/l
- Diagnosis of a ectopic pregnancy/pregnancy of unknown location
- Body surface area ≤ 1.75 m^2 but ≥1.25 m^2
- Haemoglobin between 100 and 165g/l within 3 days of treatment
- Clinically stable eg no abdominal guarding or rigidity on examination and no evidence significant of intra-abdominal bleeding on USS
- Able to understand all information and provide written informed consent

4.3 EXCLUSION CRITERIA

- Clinically significant abnormal haematological/renal/liver indices noted on pre-treatment blood test (within 3 days of treatment)
- Significant abdominal pain
- Evidence of intrauterine pregnancy
- Evidence of significant intra-abdominal bleed on USS defined by echogenic free fluid above the uterine fundus or surrounding ovary within 1 day of treatment
- EP mass on USS of greater than 3.5cm (mean dimensions) which is deemed not suitable for treatment with MTX
- Currently breastfeeding and unwilling to stop

4.4 CO-ENROLMENT

Participants will not be allowed to participate in a CTIMP or interventional non-CTIMP clinical trial until the resolution of EP (either serum hCG≤15IU/l or rescue surgery). Participants will be permitted to take part in non-interventional non-CTIMP research (e.g. questionnaires, blood collection only studies). As per ACCORD co-enrolment policy (POL008 Co-enrolment) no formal documentation or authorisation from the Sponsor is required.

5. PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Women with a diagnosis of EP suitable for medical management with MTX who wish to be considered for the study will be referred by clinical staff to the clinical research team.

5.2 CONSENTING PARTICIPANTS

Eligible participants will be approached by a member of their clinical care team and informed of the study and provided with patient information sheet. All eligible women will have the opportunity to discuss and ask questions about the study. Consent will only be taken once the patient has had adequate time to read the participant information sheet and had her questions answered. Due to the semi-emergency setting of the treatment some patients might have less than 24 hours to consider participation in the trial. Consent may be taken by a member of the clinical care team who have had specific trial training.

5.3 SCREENING FOR ELIGIBILITY

Participant eligibility will be verified by a clinical trial physician after written informed consent has been obtained. Confirmation of eligibility will be recorded within the participants' medical records.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

No further information will be collected on women who are ineligible. Individuals who are not recruited to the trial will continue with standard clinical care.

5.5 RANDOMISATION

5.5.1 Randomisation Procedure

This is a single arm open label exploratory study so no randomisation required

5.5.2 Treatment Allocation

Each trial participant will receive a single intramuscular injection of MTX (100mg) dose

5.5.3 Emergency Unblinding Procedures

The study is not blinded

5.6 WITHDRAWAL OF STUDY PARTICIPANTS

Participants are free to withdraw from the study at any point. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case report form, if possible. The participant will have the option of withdrawal from:

(i) study medication with continued study procedures and collection of clinical and safety data;

(ii) all aspects of the trial with continued use of data collected up to that point. To safeguard rights, the minimum personally-identifiable information possible will be collected.

(iii) All aspects of trial and no data collected used.

6. INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO

6.1 STUDY DRUG

6.1.1 Study Drug Identification

Methotrexate

6.1.2 Study Drug Manufacturer

Methotrexate supplied by Hospira*

6.1.3 Marketing Authorisation Holder

Hospira UK Limited

Horizon

Honey Lane

Hurley

Maidenhead

SL6 6RJ

Tel: +44 (0)1304 616161

Fax: +44 (0)1304656221

PL 04515-0038

6.1.4 Labelling and Packaging

MTX supplied by pharmacy and clinical trials labels will be put on by pharmacy staff.

Medication labels will be in the local language and comply with the legal requirements of Annex 13 of the European Union's Good Manufacturing Practice (GMP). They will include storage conditions for the drug, but no information about the patient.

6.1.5 Storage

- Do not store above 25°C. Do not freeze keep container in outer carton

6.1.6 Regulatory Release to Site

Not required.

6.1.7 Destruction of Trial Drug

Not Applicable as we using clinical stock and will be destroyed as per normal clinical practice.

6.1.8 Summary of Product Characteristics (SPC) Booklet or Investigators Brochure

The MTX Summary of Product Characteristics (SPC) (17/12/2019) (Appendix 1) is provided in a separate document with a cover sheet and signature page (signed and verified by the CI and Sponsor) and is filed in the TMF.

6.2 PLACEBO

Not Applicable

6.2.1 Labelling and Packaging

N/A

6.2.2 Storage

Not Applicable

6.3 DOSING REGIME

Single intramuscular injection 100mg/ml

6.4 DOSE CHANGES

Not Applicable

6.5 PARTICIPANT COMPLIANCE

Not Applicable

6.6 OVERDOSE

Not applicable as the dose is double checked in pharmacy before dispensing and checked by two nurses before administration to the patient.

6.7 OTHER MEDICATIONS

6.7.1 Non-Investigational Medicinal Products

Not Applicable

6.7.2 Permitted Medications

Not Applicable

6.7.3 Prohibited Medications

Not Applicable

6.8 OTHER MEDICATIONS

6.8.1 Non-Investigational Medicinal Products

Not Applicable

6.8.2 Permitted Medications

Not Applicable

6.8.3 Prohibited Medications

Not Applicable

7. STUDY ASSESSMENTS

7.1 SAFETY ASSESSMENTS

As part of routine clinical care, clinical assessments will have been carried out prior to approach into the study to assess suitability for MTX treatment and therefore suitability for the study. The results will be included and transcribed into CRF following consent:

- USS pelvis
- Serum hCG level (IU/l)
- Blood tests (FBC, LFTs, U&Es)
- Height and weight to calculate BSA

7.2 STUDY ASSESSMENTS

Study assessments on the day of treatment:

- Informed consent
- Medical history
- Eligibility (confirmed by doctor)
- Completion of case report

After the treatment, patient will follow standard clinical care until day of resolution of the EP defined as serum hCG ≤15 IU/l or surgical intervention is warranted.

Study assessments following treatment

These will follow the same pattern as the standard clinical care. Members of the clinical team or the research team will complete the trial CRF which will include:

- Adverse events
- Side effects
- Question regarding continued consent to participate in the study
- Blood tests (hCG, FBC, LFTs and U&Es) at day 4 and 7 (or when clinically taken) after the treatment and any standard care visits after day 7 (these days are indicative of normal clinical practice but may vary from patient to patient. FBC, LFTs and U&Es will only be repeated after day 7 if clinically required as per routine clinical care.
- Level of serum hCG (IU/l)

Assessment	Prior to or on the day of treatment	Standard clinical care visits: day 4 and 7 (or when clinically taken)	Standard clinical care visits after day 7
Written informed consent	☒		
Eligibility Criteria	☒		
Clinical assessment	☒	☒	☒
Continued consent		☒	☒
Serum hCG	☒	☒	☒
USS	☒		
Height and weight	☒		
FBC, U&Es, LFTs	☒	☒	
CRF completion	☒	☒	☒

7.3 COMPLIANCE ASSESSMENTS

No issues re compliance all participants will receive the IMP.

7.4 LONG TERM FOLLOW UP ASSESSMENTS

There is no long term follow up assessments after resolution of the EP.

7.5 STORAGE AND ANALYSIS OF SAMPLES

All blood samples will be analysed in NHS accredited lab as per standard care. Blood samples collected before the treatment to measure serum hCG level, FBC, LFTs and U&Es are critical for the study to determine participants' eligibility for treatment with MTX and the study.

8. DATA COLLECTION

Screening: Following consent, a member of the research team will review participant's medical history to confirm their eligibility.

Screening log: The clinical research team will keep an anonymised electronic log of women who are assessed for eligibility, are invited to participate in the study, have agreed or refused to participate and withdraw from trial. Reasons for non-recruitment (e.g. clinical decision, non-eligible) will also be recorded. The research team will also attempt to collect reasons for non-participation from women who decline to take part if they volunteer to provide this information. During the study, we will document reasons for withdrawal from the study and loss to follow-up if available.

Case Report Form: All data will be recorded on a paper CRF (pCRF) and transferred to a secure Redcap database. This will include questions to capture the baseline demographic and clinical characteristics of the participants. Data will be collected as it becomes available – i.e. at or shortly after each patient visit by members of the research team with support from the clinical care team.

If research staff is not available to see a patient during the clinical follow up visit, a member of the team will phone them at the earliest convenience to collect information about participant's wellbeing and continued consent for the study.

8.1 SOURCE DATA DOCUMENTATION

Source data is defined as all information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

Source documents are original documents, data and records where source data are recorded for the first time.

Source documents for this trial will be:

- Electronic screening log
- Researcher completed CRF
- Clinical notes
- Results from clinical tests e.g. laboratory tests, ultrasound

8.2 CASE REPORT FORMS

Case report forms will be completed in a paper format (pCRF) and collected data will be transferred to the secure Redcap database. The completed CRFs will contain information from clinical records and details of each visit. It will be used to collect information on any adverse events and side effects. Completed pCRFs will be kept secure in a locked cabinet with limited access.

All case report forms must be reviewed and approved by the ACCORD Monitor prior to use (see ACCORD SOP CR013 CRF Design and Implementation).

NOTE: All electronic case report forms are subject to Sponsor approval (see section 8.3).

8.3 TRIAL DATABASE

Each consented participant will be allocated a unique trial participant number. Data recorded on the pCRFs will be entered to the Redcap database, stored on secure server at University of Edinburgh with access limited to members of the research team. The data from the database and electronic screening log will be used for analysis of the trial and will be archived for 5 years. The archiving is a responsibility of the PI and the archived database and screening log will be kept on the servers of the University of Edinburgh.

9. DATA MANAGEMENT

9.1.1 Personal Data

The following personal data will be collected as part of the research:

- CHI number and demographic identity of the participant
- Contact details: name, address, email address, phone number

Personal data will be stored by the research team at locked cabinet with limited access in research office S7128 in Simpson Centre. The collected data will be anonymised and kept separately from the consent forms with participants' names. Electronic data collection will be stored on University of Edinburgh secure server. Personal data will be stored for minimum of 1 year. This data will be stored separately when archiving and will be placed in a sealed envelope to reduce the risk of inadvertent identification.

9.1.2 Data Information Flow

The consent form and the ID log will be the only two places where identifiable data is collected and this will be stored in the ISF with limited access. The consent form will contain the participants' name. The ID log will have a participant's hospital sticker attached which contains; name, address, CHI number and hospital number. On the ID log we will also collect telephone number and email address. The CHI, hospital number, telephone number and email will all the stored only to contact the participant for follow-up and to review clinical results. All other data collected will be anonymised. Any blood results that are collected will be transcribed in the CRF with the source remaining within the medical notes.

9.1.3 Transfer of Data

Selected anonymised data collected or generated by the study will be shared with Nordic Pharma once the study is finished. No participant can be identified by this.

9.1.4 Data Controller

For this study the data controller is the Sponsor (University of Edinburgh and NHS Lothian).

9.1.5 Data Breaches

Any data breaches will be reported to the University of Edinburgh and NHS Lothian Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

10. STATISTICS AND DATA ANALYSIS

10.1 SAMPLE SIZE CALCULATION

This is a pilot study to look at patient acceptability and safety. We will collect preliminary data on the safety profile of the 100 mg dose. A population study (n=54 patients) analysing 10 haematological and biochemical safety parameters after methotrexate administration showed

that serum alanine aminotransferase (ALT) was the best safety marker. Routine methotrexate administration was associated with a 19.75 iu/l (95% CI: 4.35 – 35.15) increase in serum ALT concentrations (+117.14%). The next most accurate safety marker was white blood cell count, which was associated with a 1.2 x109/l (95% CI: 0.74 – 1.66) reduction (-15.51%). Recruiting 10 patients would be required to determine if there was a 70 iu/l increase in ALT, which was thought to be clinically significant, with an alpha of 0.05 and a power of 80%. This would be able to detect a 2.8 x109/l decrease in WCC which would take the WCC to 3.3 x109 that is below the normal range, which would be considered clinically significant, with an alpha of 0.05 and a power of 80%. At the Royal Infirmary of Edinburgh, based on a conversion rate of 59% in GEM3 (clinical trial recruiting patients with EP who receive treatment with MTX) it is estimated that 17 women will need to be approached.

11. PHARMACOVIGILANCE

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

Full details of contraindications and side effects that have been reported following administration of the IMP can be found in the relevant MTX: SPC (Appendix 1)
Participants will be instructed to contact their Investigator at any time after consenting to join the trial if any symptoms develop. All AEs and SAEs will be recorded from the time a participant signs the consent form to take part in the study until seven days post-methotrexate administration, if surgery takes place during the first week. If surgery occurs after the first seven days of methotrexate administration then AEs and SAEs will be recorded until date of surgery or hCG ≤15 iu/l, whichever comes first. AEs must be recorded in the AE log within the Case Report Form (CRF). In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment.

11.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An **adverse reaction** (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that at any dose:

- results in death of the clinical trial participant;
- is life threatening*;
- requires in-patient hospitalisation^ or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

*Life-threatening in the definition of an SAE or SAR refers to an event where the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

^Any hospitalisation that was planned prior to enrolment will not meet SAE criteria. Any hospitalisation that is planned post enrolment will meet the SAE criteria.

A suspected unexpected serious adverse reaction (SUSAR) is any AR that is classified as serious and is suspected to be related to the IMP, that it is not consistent with the information about the IMP in the Summary of Product Characteristics (SPC) booklet or Investigators Brochure.

11.2 IDENTIFYING AEs AND SAEs

Participants will be asked about the occurrence of AEs/SAEs at every visit during the study. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence. Participants will also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded.

AEs and SAEs may also be identified via information from support departments e.g. laboratories.

Known side effects of the MTX when used to treat EP will be noted on the CRFs but not recorded as AEs,

- Ulcerative stomatitis (mouth ulcers)
- Leukopenia
- Nausea
- Abdominal distress
- Skin rashes (Erythematous rashes, Urticaria, Dermatitis
- Hepatic toxicity resulting in raised elevations of liver enzymes (out with normal range)
- Dizziness
- Pain
- Fatigue
- Vomiting
- Diarrhoea
- Loss of appetite
- Headache
- Bloating
- Flatulence

unless meeting seriousness criteria. If they reach criteria of SAE they will be recorded on the AE log within the CRF and reported to sponsor as SAE.

Events not to be reported as SAEs as hospitalisation for these events is an expected event within this population group.

1. Admittance to hospital for surgery related to EP
2. Admittance to hospital for monitoring of EP
3. Admittance to hospital for monitoring of EP pain

11.3 RECORDING AEs AND SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator, or another suitably qualified physician in the research team who is delegated to record and report AEs/SAEs, to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator will then record all relevant information in the CRF/AE log and on the SAE form (if the AE meets the criteria of serious).

Information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

All AEs and SAEs will be recorded from the time a participant signs the consent form to take part in the study until seven days post-methotrexate administration, if surgery takes place during the first week. If surgery occurs after the first seven days of methotrexate administration then AEs and SAEs will be recorded until date of surgery or hCG ≤15 iu/l, whichever comes first.

11.3.1 Pre-existing Medical Conditions

Pre-existing medical conditions (i.e. existed prior to informed consent) should be recorded as medical history and only recorded as adverse events if medically judged to have worsened during the study.

Hospitalisation for treatment planned and for elective treatment of a pre-existing condition will not be reported as SAE but will be recorded on the concomitant procedure page of the CRF.

11.3.2 Worsening of the Underlying Condition during the Trial

Medical occurrences or symptoms of deterioration that are expected due to the participant's underlying condition should be recorded in the patient's medical notes and only be recorded as AEs on the AE log if medically judged to have unexpectedly worsened during the study.. Events that are consistent with the expected progression of the underlying disease should not be recorded as AEs.

Admittance to hospital for surgery or monitoring of EP will not be considered as an SAE. All AEs and SAEs will be recorded from the time a participant signs the consent form to take part in the study until seven days post-methotrexate if surgery takes place during the first week, if after the first seven days, date of surgery or hCG ≤15 iu/l, whichever comes first.

11.4 ASSESSMENT OF AEs AND SAEs

Each AE must be assessed for seriousness, causality, severity and ARs must be assessed for expectedness by the Principal Investigator or another suitably qualified physician in the research team who has been delegated this role.

For randomised double blind studies, AEs will be assessed as though the participant is taking active IMP. SUSARs will be unblinded by ACCORD before they are reported to REC and CA (by ACCORD).

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

11.4.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness.

11.4.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the IMP according to the definitions below.

- Unrelated: where an event is not considered to be related to the IMP.
- Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study drug.

Where non Investigational Medicinal Products (NIMPs) e.g. rescue/escape drugs are given: if the AE is considered to be related to an interaction between the IMP and the NIMP, or where the AE might be linked to either the IMP or the NIMP but cannot be clearly attributed to either one of these, the event will be considered as an AR. Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated.

11.4.3 Assessment of Expectedness

If the event is an AR the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the SPC booklet

The event may be classed as either:

Expected: the AR is consistent with the toxicity of the IMP listed in the SPC booklet.

Unexpected: the AR is not consistent with the toxicity in the SPC booklet

Fatal and life threatening SARs should usually be considered unexpected. Fatal SARs can only be expected for IMPs with an MA in the EU, when it is clearly stated in the list of ARs of the SPC (Section 4.8) that the IMP causes fatal SARs.

11.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE/SAR/SUSAR and record this on the CRF/AE log or SAE form according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.

Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

11.5 RECORDING OF AEs

All adverse events for each participant will be recorded on the AE log and will be assigned the appropriate MedDRA Systems Organ Class (SOC) code.

11.6 REPORTING OF SAEs/SARs/SUSARs

Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD Research Governance ***within 24 hours****. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.*

The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 11.4.2, Assessment of Causality and 11.4.3, Assessment of Expectedness.

The SAE form will be transmitted via email to safety@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. Forms may also. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

All reports sent to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

Side effects and AEs/SAEs will be recorded on the CRF and the database.

SAEs will be reviewed quarterly by ACCORD independent assessors.

11.7 REGULATORY REPORTING REQUIREMENTS

ACCORD is responsible for pharmacovigilance reporting on behalf of the co-sponsors (The University of Edinburgh and NHS Lothian).

ACCORD has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the trial). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD (or delegate) will inform Investigators at participating sites of all SUSARs and any other arising safety information.

ACCORD will be responsible for providing safety line listings and assistance; however, it is the responsibility of the Investigator to prepare the Development Safety Update Report. This annual report lists all SARs and SUSARs reported during that time period. The responsibility of submitting the Development Safety Update Report to the regulatory authority and RECs, lies with ACCORD.

11.8 FOLLOW UP PROCEDURES

After initially recording an AE or recording and reporting an SAE, the Investigator should make every effort to follow each event until a final outcome can be recorded or reported as necessary. Follow up information on an SAE will be reported to the ACCORD office.

If, after follow up, resolution of an event cannot be established, an explanation should be recorded on the CRF or AE log or additional information section of SAE form.

11.9 PREGNANCY

All participants are pregnant at the time of enrolment therefore there will be no pregnancy reporting for this study.

12. TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

12.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Project Management Group, consisting of the grant holders (Chief Investigator and Principal Investigator in Edinburgh), A Trial Manager and coordinating nurse.

The Trial Manager will oversee the study and will be accountable to the Chief Investigator. The Trial Manager will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

12.2 TRIAL STEERING COMMITTEE

No Trial Steering Committee will be established as this is a small exploratory study with a short recruitment period.

12.3 DATA MONITORING COMMITTEE

No Data Monitoring Committee will be established as this study is a small exploratory study of a well-known drug. The core research team will monitor any AEs on a 2 weeks basis.

12.4 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

12.5 RISK ASSESSMENT

A study specific risk assessment will be performed by representatives of the co-sponsors, ACCORD monitors and the QA group, in accordance with ACCORD governance and sponsorship SOPs. Input will be sought from the Chief Investigator or designee. The outcomes of the risk assessment will form the basis of the monitoring plans and audit plans. The risk assessment outcomes will also indicate which risk adaptions could be incorporated into to trial design.

12.6 STUDY MONITORING AND AUDIT

ACCORD clinical trial monitors, or designees, will perform monitoring activities in accordance with the study monitoring plan. This will involve on-site visits and remote monitoring activities as necessary. ACCORD QA personnel, or designees, will perform study audits in accordance with the study audit plan. This will involve investigator site audits, study management audits and facility (including 3rd parties) audits as necessary (delete where not required).

13. GOOD CLINICAL PRACTICE

13.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

13.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

13.3 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

13.3.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any study specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s).

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The original will be signed in the Investigator Site File (ISF). The participant will receive a copy of the signed consent form and a copy will be filed in the participant's medical notes.

13.3.2 Study Site Staff

The Investigator must be familiar with the IMP, protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the IMP, protocol and their trial related duties.

13.3.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

13.3.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the ACCORD Research Governance & QA Office, including but not limited to:

- An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents);

- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.
- ACCORD will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF) or Sponsor File, where required. The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs. Under certain circumstances the TMF responsibilities may be delegated to the research team by ACCORD. The TMF for this trial will be stored and maintained by the Sponsor, in accordance with SOP CR001

13.3.5 GCP Training

All study staff must hold evidence of appropriate GCP training.

13.3.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

13.3.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including where applicable the General Data Protection Regulation with regard to the collection, storage, processing and disclosure of personal information. Access to personal information will be restricted to individuals from the research team treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

14. STUDY CONDUCT RESPONSIBILITIES

14.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Proposed amendments will be submitted to the Sponsor for classification and authorisation.

Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to implementation.

14.2 PROTOCOL NON COMPLIANCE

14.2.1 Definitions

Deviation - Any change, divergence, or departure from the study design, procedures defined in the protocol or GCP that does not significantly affect a subjects rights, safety, or well-being, or study outcomes.

Violation - A deviation that may potentially significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being

14.2.2 Protocol Waivers

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

14.2.3 Management of Deviations and Violations

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation.Deviation logs / violation forms will be transmitted via email to QA@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be sent by fax to by submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

14.3 URGENT SAFETY MEASURES

The Investigator may implement a deviation from or change to the protocol to eliminate an **immediate hazard** to trial participants without prior approval from the REC and the MHRA. This is defined as an urgent safety measure and the investigator must contact the Clinical Trial Unit at the MHRA and discuss the issue with a medical assessor immediately (+44 (0) 20 3080 6456).

The Investigator will then notify the MHRA (clintrialhelpline@mhra.gsi.gov.uk), the REC and ACCORD, in writing of the measures taken and the reason for the measures within 3 days by submitting a substantial amendment.

14.4 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (QA@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to regulatory authorities and research ethics committees as necessary.

14.5 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

14.6 END OF STUDY

The end of study is defined as the last participant's last visit

The Investigators and/or the trial steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, Regulatory Authority, R&D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot.

In accordance with ACCORD SOP CR011, a Clinical Study Report (CSR) will be provided to the Sponsor (QA@accord.scot) and REC within 1 year of the end of the study.

Upon completion of the study, the Investigator will upload clinical trial results onto the EudraCT database on behalf of the Sponsor.

The Investigator will submit a short confirmatory e-mail to the MHRA (CT.Submission@mhra.gsi.gov.uk) once the result-related information has been uploaded to EudraCT, with 'End of trial: result-related information: EudraCT XXXX-XXXXXX-XX' as the subject line. The Sponsor(s) will be copied in this e-mail (QA@accord.scot). It should be noted that you will not get an acknowledgment e-mail or letter from the MHRA.

14.7 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

Due to the nature of the condition and management strategy there is no requirement to continue the treatment after the resolution of the EP.

14.8 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been authored by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities. Sites which are part of the United Kingdom's National Health Service have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.
- The manufacturer supplying IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

15. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

15.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

15.2 PUBLICATION

The Clinical Study Report (CSR) will be submitted to the Sponsor and REC within 1 year of the end of the study. Where acceptable, a published journal article may be submitted as the CSR. The Chief Investigator will provide the CSR to ACCORD, for review, prior to finalization. The clinical study report may be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. The results of the study, together with other mandated information, will be uploaded to the European clinical trials database within 1 year of the end of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion).

15.3 DATA SHARING

Anonymised data and the results of the study will be shared with Nordic Pharma

15.4 PEER REVIEW

This project has been internally reviewed by the trial management team and staff members form Nordic Pharma.

16. REFERENCES

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2. National Collaborating Centre for Ws, Children's H. National Institute for Health and Clinical Excellence: Guidance. Ectopic Pregnancy and Miscarriage: Diagnosis and Initial Management in Early Pregnancy of Ectopic Pregnancy and Miscarriage. London: Rcog Copyright © 2012, National Collaborating Centre for Women's and Children's Health.; 2012.
3. Barnhart KT, Gosman G, Ashby R, Sammel M. The medical management of ectopic pregnancy: a meta-analysis comparing "single dose" and "multidose" regimens. Obstet Gynecol. 2003;101(4):778-84.