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Treatment of postpartum haemorrhage

Submission date
13/12/2023

Recruitment status
Recruiting

Registration date
18/03/2024

Overall study status
Ongoing

Last Edited
30/04/2024

Condition category
Pregnancy and Childbirth

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
This is a phase III, randomised, double-blind, multicentre, international trial aiming to evaluate the efficacy and safety of heat-stable carbetocin (HSC) for treatment of postpartum haemorrhage (PPH) in women who have had a vaginal birth.

Who can participate?
Women with vaginal births who have received HSC as prevention for PPH.

What does the study involve?
6,200 participating women will be randomised to receive either intravenous HSC or oxytocin as the 'first-line' PPH treatment. Once administered, the clinical staff will continue further PPH management in accordance with existing hospital PPH management protocol and WHO guidelines.
All women will be followed up for 24 hours after randomisation or until hospital discharge, whichever is soonest.
The trial will be conducted across Argentina, Kenya, India, Nigeria, Uganda, South Africa, and United Kingdom. Recruitment for the trial will occur over 30 months.

What are the possible benefits and risks of participating?
Benefits:
Participants will personally not benefit from taking part in the study. While taking part in the study, participants will be monitored more closely than if they were not in a research study. By participating participants may be helping to identify the best medicine to treat severe postpartum bleeding in the future.
Risks:
We do not expect that the study medicine (HSC) will produce different side effects from the ones caused by the Oxytocin medicine that the doctors would normally use, which are abdominal pain or discomfort, nausea or vomiting.

There is a small chance that HSC can cause changes in heart rate and reduce blood pressure. However, when this was checked in a large global study, there was no difference in the number of people experiencing changes in heart rate or reduction in blood pressure, between HSC and Oxytocin (which is used currently for treatment).

HSC is very similar to Oxytocin, and so we do not expect that two doses of HSC will produce different side effects from the ones caused by two doses of Oxytocin, which are commonly and safely used in routine care. We have also already tested giving two doses of the study medicine (HSC) to a small group of women and no concerns were reported. The results were checked by a group of international safety experts.

We will be following participants closely and will keep track of any unwanted effects or problems. We may use some other medicines to decrease the pain or discomfort. If this is necessary, we will discuss this with participants prior to administration.

The known side effects, risks and discomforts are detailed in the Main Participant Information Sheet, so participants are able to make an informed decision on whether or not they would like to take part.

Where is the study run from?
World Health Organization (Switzerland)

When is the study starting and how long is it expected to run for?
December 2023 to June 2028

Who is funding the study?
World Health Organization (Switzerland)

Who is the main contact?
Dr Femi Oladapo, oladapoo@who.int

Contact information

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Integrated Research Application System (IRAS)
1009137

Protocol serial number
A66045

Study information

Scientific Title
Heat-stable carbetocin for the treatment of postpartum haemorrhage: a phase III, randomized, double-blind, active controlled, multicountry, multicentre, non-inferiority trial

Acronym
REACH

Study objectives
The main aim of this trial is to generate evidence on the efficacy and safety of Heat-stable carbetocin (HSC) compared to oxytocin when used as ‘first-line’ uterotonic for Postpartum Haemorrhage (PPH) treatment. The primary objective of this trial is to evaluate whether HSC is non-inferior to oxytocin for treatment of PPH in women who receive HSC for PPH prophylaxis, in the prevention of additional blood loss of 500 ml or more at 90 min following randomization.

There are two hypotheses for the primary objective (one non-inferiority and one superiority hypotheses):
1. Intravenous (IV) HSC is non-inferior to IV oxytocin in terms of the proportion of women with PPH experiencing additional blood loss of 500 ml or more within a non-inferiority margin of 4% risk difference scale (primary hypothesis).
2. Intravenous (IV) HSC is superior to IV oxytocin in terms of the proportion of women with PPH experiencing additional blood loss of 500 ml or more (secondary hypothesis).

The secondary objectives are to (i) evaluate the comparative effects of HSC versus oxytocin on haemodynamic outcomes when used for PPH treatment in women receiving HSC for prophylaxis; and (ii) evaluate the cost-effectiveness of the PPH treatment with HSC compared to PPH treatment with oxytocin, if HSC is proven non-inferior.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 16/02/2024, West Midlands - Edgbaston Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8357; edgbaston.rec@hra.nhs.uk), ref: 24/YH/0005

Primary study design
Interventional

Study design
Interventional randomized controlled trial

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Postpartum haemorrhage (PPH)

Interventions
This is a phase III, randomised, double-blind, multicentre, international trial aiming to evaluate the efficacy and safety of heat-stable carbetocin (HSC) for treatment of postpartum haemorrhage (PPH) in women who have had a vaginal birth. 6,200 participating women with vaginal births who have received HSC as prevention for PPH, will be randomised to receive either intravenous HSC or oxytocin as the 'first-line' PPH treatment. Once administered, the clinical staff will continue further PPH management in accordance with existing hospital PPH management protocol and WHO guidelines.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
HSC – Heat-Stable Carbetocin, oxytocin

Primary outcome(s)
Proportion of women with additional vaginal blood loss of ≥ 500 ml at 90 minutes following randomisation.

Key secondary outcome(s)
Key secondary endpoints:
1. Additional blood loss of ≥ 1000 ml at 90 minutes following randomisation
2. Use of additional uterotonic(s) at 90 minutes following randomisation
3. Additional blood loss of ≥ 500 ml OR use of additional uterotonic(s) at 90 minutes following randomisation
4. Use of surgical procedure(s) related to PPH (uterine balloon tamponade, laparotomy for either compressive sutures, artery ligation or hysterectomy) as at 24 hours following randomisation
5. Occurrence of clinically significant cardiac arrhythmia based on clinical judgement which requires treatment up to 24 hours.

Other secondary end-points:
6. Amount of blood loss at 90 minutes following randomisation
7. Use of additional uterotonics as at 24 hours following randomisation
8. Use of blood transfusion products as at 24 hours following randomisation
9. Admission to intensive care unit as at 24 hours following randomisation

10. Maternal death
11. Clinically defined coagulopathy as at 24 hours following randomisation
12. Breastfeeding as at 24 hours following randomisation
13. Occurrence of shock up to 24 hours following randomisation
14. Frequency and severity of adverse or serious adverse events as at 24 hours following randomisation
15. Composite outcome of maternal death or severe morbidity as at 24 hours following randomisation
16. Any haemodynamic change requiring therapeutic intervention during the 10 minutes of initiating treatment infusion
17. Occurrence of clinically significant cardiac arrhythmia based on clinical judgement which requires treatment in the first 10 minutes after initiating treatment infusion
18. Occurrence of clinically significant cardiac arrhythmia based on clinical judgement which results in cardiac arrest during the first 24 hours following randomisation

End-points specific to the safety substudy:
1. Reduction in mean arterial pressure (MAP) of > 20% from baseline in the first 5 minutes from the start of treatment infusion (main endpoint).
2. Persistent fall of MAP of > 20% from baseline for a further 5 minutes during the first 5 minutes after start of infusion
3. Any haemodynamic change requiring therapeutic intervention (e.g. fluid administration or vasopressors/inotropes) for a 30-minute period from the start of the treatment infusion).
4. MAP of 60 mmHg or less in the first 5 minutes after start of treatment infusion
5. MAP at 5, 10 minutes following start of infusion.
6. Tachycardia defined as occurrence of a persistent increase in heart rate >30% from baseline for 30 minutes after start of treatment infusion.
7. Heart rate at 5 and 10 minutes following start of treatment infusion.
8. Bradycardia defined as occurrence of heart rate less than 50 beats per minute for any duration of time within the 30-minute period from the start of the treatment infusion
9. Reduction in mean arterial pressure (MAP) of >20% for a 180 -minute period from the start of the treatment infusion.
10. Area under the curve (AUC) MAP for 30-minute period from the start of the treatment infusion.
11. Mean heart rate for a 30-minute period from the start of the treatment infusion.
12. Tachycardia defined as occurrence of a persistent increase in heart rate >120/minute for a 30-minute period from the start of the treatment infusion.
13. Any cardiac arrhythmia (beyond tachycardia and bradycardia outlined above) for a 30-minute period from the start of the treatment infusion.
14. Any safety and tolerability events including chest pain, myocardial ischemia, ST changes and /or QT prolongation for each woman for a 30-minute period from the start of the treatment infusion.
15. Frequency and severity of maternal adverse events (including nausea/vomiting, flushing or headaches) for a 30-minute period from the start of the treatment infusion.
16. Frequency and severity of serious adverse events for each woman for a 30-minute period from the start of the treatment infusion.
17. Composite outcome of maternal death, cardiac arrest or severe morbidity for 24 hours following randomisation.

Completion date
30/06/2028

Eligibility

Key inclusion criteria
1. Had a singleton pregnancy
2. Had a vaginal birth
3. Receive HSC for PPH prophylaxis during the vaginal birth
4. Have an indication to receive uterotonics for the first response treatment of PPH presumably due to uterine atony (clinically diagnosed, or measured blood loss of 500 ml or more from the vagina, and where known coagulopathy and retained placenta has been excluded as the cause of bleeding)
5. Provided written informed consent before any trial-related procedures are carried out.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
10 Years

Sex
Female

Key exclusion criteria
1. Known history of allergy to HSC or oxytocin or excipients in the medicinal products used in the trial
2. Known serious coagulopathy, epilepsy, hepatic, renal, or cardiovascular disease
3. Known intrauterine foetal death
4. Birth that is considered an abortion according to local gestational age limit
5. Other clinically significant condition(s) that, in the opinion of the investigator could represent increased health risk for the participation of the woman or interfere with the objectives of the trial
6. A manual removal of placenta
7. A placenta in-situ that has not been expelled or removed
8. Known administration of any uterotonic for PPH treatment (e.g. prostaglandins, oxytocin, ergometrine) following PPH prophylaxis.

Date of first enrolment
01/03/2024

Date of final enrolment
31/05/2028

Locations

Countries of recruitment

United Kingdom

Argentina

India

Kenya

Nigeria

South Africa

Uganda

Study participating centre
University Hospitals Coventry and Warwickshire NHS Trust
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Sponsor information

Organisation
World Health Organization

ROR
https://ror.org/01f80g185

Funder(s)

Funder type
Other

Funder Name
World Health Organization

Alternative Name(s)
, , Всемирная организация здравоохранения, Organisation mondiale de la Santé, Organización Mundial de la Salud, WHO, , BO3, OMS

Funding Body Type

Government organisation

Funding Body Subtype
International organizations

Location
Switzerland

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.
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IPD sharing plan summary
Data sharing statement to be made available at a later date