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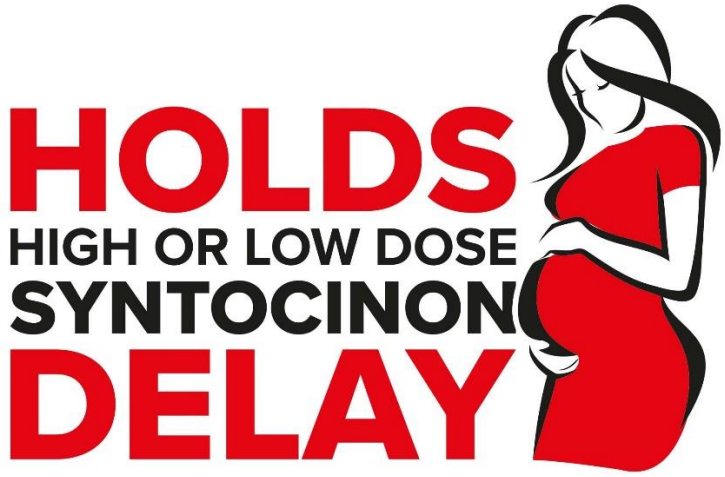

High Or Low Dose Syntocinon for delay in labour

Trial Protocol

Version 9.0 dated 10th October 2022

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NHS Birmingham Women's and Children's NHS Foundation Trust

CI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

This protocol has been approved by:

Trial Name:	The HOLDS Trial
Protocol Version Number:	9.0
Protocol Version Date:	10th October 2022
Chief Investigator Name:	Sara Kenyon
Signature and date:	 10-Oct-2022
Team Leader Name:	Clive Stubbs
Signature and date:	 10-Oct -2022
Trial Statistician Name:	Lee Middleton
Signature and date:	 10-Oct -2022

Sponsor Statement:

As formally delegated by Birmingham Women's and Children's NHS Foundation Trust, the Sponsor confirms approval of this protocol.

Compliance Statement:

This protocol describes the HOLDS Trial only. The protocol should not be used as a guide for the treatment of participants not taking part in the HOLDS Trial.

The study will be conducted in compliance with the approved protocol, UK Policy Framework for Health and Social Care Research 2017, the Data Protection Act 2018, and the Principles of Good Clinical Practice as defined by the European Good Clinical Practice (GCP) Directive. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

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1 Trial Summary

Title

High Or Low Dose Syntocinon (known as oxytocin) for delay in labour (HOLDS).

Settings

Obstetric departments in approximately 30 hospitals within the UK.

Trial Design

Multicentre, randomised, double blind controlled trial of 1500 nulliparous women with delay in labour and ruptured membranes.

Aims

Primary objective:

- To perform a robust multicentre, randomised, double blind controlled trial to evaluate the effect on CS (caesarean section) rate of high dose regimen versus standard dose regimen oxytocin for nulliparous women at term (gestation of 37+0 - 41+6) with confirmed delay in the first stage of labour using NICE definitions.

Secondary objectives:

- To assess the effect on maternal and neonatal outcomes.
- To explore any variation in effect in women randomised with cervical dilation <6cm and >=6cm.
- To assess the safety of high dose oxytocin. Oxytocin can cause excess contractions (tachysystole) which can cause abnormalities of the fetal heart rate (hyperstimulation) and we will collect information regarding safety for both women and babies.

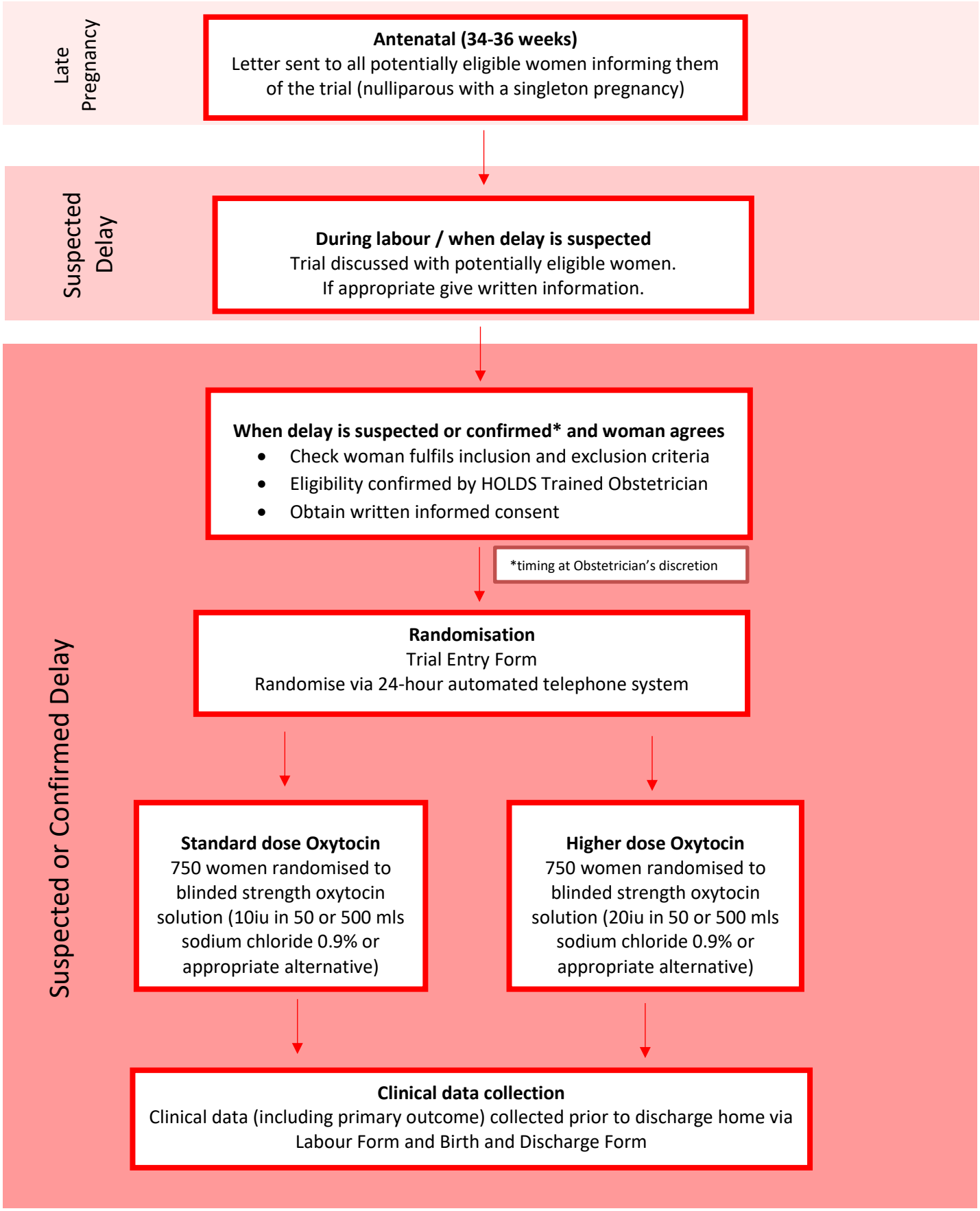
Target Population

Nulliparous women with a singleton cephalic pregnancy at term (gestation of 37+0 - 41+6) with delay in labour and ruptured membranes for whom the clinical decision has been made to prescribe oxytocin for augmentation of labour.

Health Technologies Assessed

Standard dose regimen of oxytocin (2mU/min increasing every 30 minutes to a maximum 32mU/min) compared with high dose regimen (4mU/min increasing every 30 minutes to a maximum of 64mU/min).

2 Trial Schema



3 Lay Summary

We currently do not know the best care for first time mothers with delayed progress in the first stage of labour and this topic is a research priority for the Royal College of Obstetricians and Gynaecologists. Delayed labour is a relatively common occurrence affecting between 11- 30% (equivalent to between one and three in ten) of first time mothers.

The only recommended treatment for women delayed in the first stage of labour is artificial oxytocin (Syntocinon) which is given intravenously to stimulate contractions. A standard regimen (concentration and rate of administration) is recommended by NICE Guidelines 2014 and is widely used in the UK. Information from studies looking at different dose regimens of oxytocin in delayed labour suggest that a high dose regimen may reduce the chance of Caesarean section but the available evidence is not conclusive. Oxytocin may cause the uterus to contract too much and the baby to become distressed so both mother and baby are carefully monitored and the dose adjusted in relation to the number of contractions and how the baby is.

Research shows currently around 32% (equivalent to about three in ten) of the women who need oxytocin for delayed labour have an unplanned Caesarean section, which we know is related to a longer hospital stay, higher risk of infection, bleeding and blood clots and to increase risk of Caesarean section in future pregnancies. By reducing Caesarean section we can reduce these risks to women. A reduction in the Caesarean section rate of 5-8% (equivalent to nearly one in ten) in these women could save the NHS nearly £1M per year, as well as possible annual savings of £2.6M from the impact of avoiding Caesarean section in future pregnancies.

Our trial will randomise 1500 women to standard or high dose regimens of oxytocin and measure differences in rates of caesarean section as well as collecting information about the birth and safety of mother and baby. Clinicians will not be aware of which regimen of oxytocin is being given, and care will be the same for either group. Serious adverse events are more likely in this high risk group of women and these will be reviewed by an independent group (Data Monitoring Committee).

Recruiting women to clinical trials in labour is challenging, and in our pilot study we showed that informing all potentially eligible women about the study in late pregnancy , and approaching them during labour to discuss the study is acceptable. We have set a realistic target for recruitment of about 20% (equivalent to one in five) of eligible women, based on the pilot and realise the importance of training staff so they can explain the study and answer any questions women and their partners may have.

This study brings together a multidisciplinary team of experts-academics, clinicians, statisticians, and a service user, who together have successfully undertaken the pilot study. Information from this study will directly influence care of future women with delayed labour.

4 Contacts and Roles

4.1 Sponsor and Sponsor Roles

Birmingham Women's and Children's NHS Foundation Trust (BWCNFT) is the sponsor of HOLDS. The BWCNFT is responsible for obtaining necessary approvals and for governance. The Trial Management Group is jointly responsible for overseeing good clinical practice and the Principal Investigators are responsible for obtaining informed consent and care of the participants.

4.2 Trials Office

The University of Birmingham Clinical Trials Unit (BCTU)
Institute of Applied Health Research, University of Birmingham, Birmingham B15 2TT

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Lead Midwife Telephone: 07816 363 582

Website: www.birmingham.ac.uk/holds

Trial database: www.trials.bham.ac.uk/HOLDSstudy/

All queries should be directed to the HOLDS Trials Office in the first instance.

FOR RANDOMISATION

TELEPHONE: 0800 2802 307 (UK)

4.3 HOLDS Trial Management

Chief Investigator (CI)

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Sponsor Representative

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  Birmingham Women's and Children's NHS Foundation Trust
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- Professor Peter Brocklehurst, BCTU Director of Research and Development, Birmingham Clinical Trials Unit
- Mr Lee Middleton, Senior Medical Statistician, Birmingham Clinical Trials Unit
- Ms Versha Cheed, Medical Statistician, Birmingham Clinical Trials Unit

Trial Management

- Trial Management Team Leader: Mr Clive Stubbs, Birmingham Clinical Trials Unit
- Senior Trial Manager: Mrs Dee Wherton, Birmingham Clinical Trials Unit
- Trial Manager: Ms Afreen Khan, Birmingham Clinical Trials Unit
- Research Midwife: Mrs Kate Siddall, Birmingham Women's and Children's NHS Foundation Trust
- Senior Data Manager: Mr Jack Toland, Birmingham Clinical Trials Unit
- Data Manager: Scott Phillips, Birmingham Clinical Trials Unit

Clinical Co-Applicants

- Dr Tracey Johnston, Consultant in Fetal Maternal Medicine
- Mr Kim Hinshaw, Consultant Obstetrician and Gynaecologist
- Dr Jason Waugh, Consultant in Obstetrics and Maternal Medicine
- Professor Julia Sanders, Professor of Clinical Nursing and Midwifery
- Professor Andrew Ewer, Professor of Neonatal Medicine

Non-Clinical Co-Applicants

- Ms Ruth Hewston, PPIE Representative
- Ms Louise Jackson, Lead Health Economist

4.4 Trial Steering Committee (TSC)

- Professor Steve Thornton, Consultant Obstetrician (Chair)
- Professor Deirdre Murphy, Professor of Obstetrics (Clinical Member)
- Professor Debra Bick, Professor of Clinical Trials in Maternal Health (Clinical Member)
- Ms Jennifer Holly, Research and Evaluation Manager for the National Childbirth Trust (PPIE Representative)
- Professor Declan Devane, Professor of Midwifery (Clinical Member)
- Ms Trish Hepburn, Senior Statistician (Statistician)

4.5 Data Monitoring Committee (DMC)

For interim analysis and response to specific concerns

- Professor Derek Tuffnell, Retired Consultant Obstetrician and Gynaecologist and Lead Obstetrician for Research (Chair)
- Dr David Cooper, Statistician (Statistician)
- Dr Vikki Smith, Senior Lecturer (Clinical Member)

5 Abbreviations

AE	Adverse event
APR	Annual Progress Report
AR	Adverse reaction
BCTU	Birmingham Clinical Trials Unit (at the University of Birmingham)
BWCNFT	Birmingham Women's and Children's NHS Foundation Trust
CHaRT	Centre for Healthcare Randomised Trials
CI	Chief Investigator
CRF	Case Report Form
CRN	Clinical Research Network
CS	Caesarean section
CTIMP	Clinical Trial of an Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
FBS	Fetal blood sampling
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
GP	General Practitioner
HDU	High Dependency Unit
HTA	Health Technology Assessment
ICH GCP	International Committee on Harmonisation Good Clinical Practice
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
ITU	Intensive Therapy Unit
IU	International Units
IV	Intravenous
MHRA	Medicines and Healthcare products Regulatory Agency
mU	Milliunits
NCT	National Childbirth Trust
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NNU	Neonatal Unit
PI	Principal Investigator

PIL	Participant Information Leaflet
PPI	Patient and Public Involvement
REC	Research Ethics Committee
RR	Relative Risk
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SOeCAT	Schedule of Events Cost Attribution Template
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVB	Spontaneous vaginal birth
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
WHO	World Health Organisation

6 Background

HOLDS Is a multicentre, double-blind randomised controlled trial to evaluate whether a high dose regimen oxytocin for nulliparous women delayed in the first stage of labour reduces the Caesarean section (CS) rate. These women have a relatively high rate of unplanned CS[1] (34%) and making sure the rate is as low as possible is important as unplanned CS is associated with longer stay in hospital, higher risk of infection, bleeding and blood clots and is associated with an increased risk of CS in subsequent pregnancies[2,3,4].
Robust evidence as to how best to care for women with delayed labour is lacking and it is a research priority for the Royal College of Obstetricians and Gynaecologists (RCOG). The length of labour for nulliparous women is on average 8 hours and it is unlikely to last over 18 hours[5]. In line with NICE guidance[5] once a woman is in established labour (i.e. she has regular painful contractions and her cervix is 4cm or more dilated on examination) assessment of progress includes cervical dilation as well as descent and rotation of the baby's head and changes in the strength, duration and frequency of uterine contractions. Should delay be suspected (when cervical dilation of <2cm in four hours is found) the woman remains under the care of a midwife, providing all other parameters remain normal. During the two hour period until progress is re-assessed the midwife is likely to suggest interventions which would facilitate progress occurring. The midwife caring for the woman would encourage the woman to mobilise, consider hydration (e.g. a sports drink), and discuss appropriate and effective pain relief. If her membranes are still intact, artificial rupture (amniotomy) will also be advised. Once delay is confirmed if cervical progress < 1cm found on re-assessment, transfer to obstetric-led care would take place (if required) for an obstetric review and a decision about management options. There are some situations when waiting another 2 hours is not appropriate, for example if there are few uterine contractions. The clinical team will discuss these individual circumstances and may recommend treatment starts sooner.

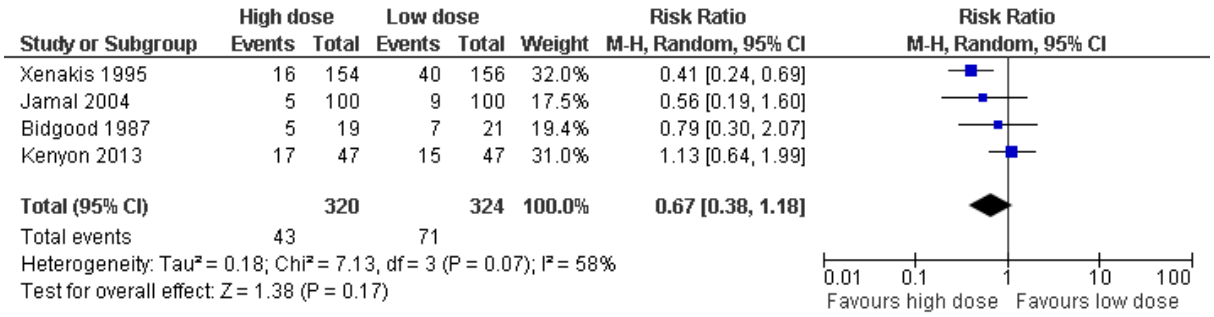
The only recommended treatment is Syntocinon (known as oxytocin) which is an inexpensive licensed synthetic version of the hormone oxytocin. It is routinely given by intravenous infusion to stimulate contractions leading to birth.

6.1 Evidence for the dose regimen of oxytocin

The current standard regimen of oxytocin for confirmed delay[6] suggests a starting dose of 1-2 mU/minute and increase intervals of 30 minutes or more to a maximum of 32mU/minute. This is given to increase the frequency and strength of uterine contractions with the aim that vaginal birth will be achieved. There is recent evidence from two systematic reviews that higher dose regimens (both of rate and strength) of oxytocin than currently recommended may decrease CS and increase vaginal birth rates, although there is insufficient evidence to recommend a change in practice.

The first review considered women delayed in normal labour (Cochrane Systematic Review[7]) comparing high versus low dose oxytocin regimens. The authors defined high dose oxytocin as a starting dose and increments >4mU/minute and low dose as a starting dose 1-4 mU/minute and increments of 1-2 mU/minute. The review included four trials and 644 women and showed a reduction in the risk of CS (RR 0.62; 95% CI 0.44 to 0.86) in favour of high dose regimen, although removing one trial at high risk of bias increased the uncertainty (RR: 0.89; 95%CI: 0.57 to 1.38; p=0.6). Even attempting to account for the heterogeneity using a random effects model which some would suggest was more appropriate[8] resulted in an estimate that was not statistically significant (RR: 0.67; 95%CI: 0.38 to 1.18; p=0.2) (see *Figure 1*).

Figure 1. Forest plot demonstrating effect of high and low dose oxytocin on caesarean section.



Similarly, there was no convincing evidence that a difference was seen in spontaneous vaginal birth rate due to doubts with the same trial and there were no differences noted in other outcomes: instrumental vaginal birth, epidural analgesia, hyper-stimulation, postpartum haemorrhage, chorioamnionitis or women's perceptions of experience.

The second review[9] used similar definitions for oxytocin dose regimens (starting doses and increments of above and below 4mU/minute). Although results demonstrated high dose oxytocin regimens were associated with a reduction in the risk of CS this was in a mixed population. Ten randomised trials (5423 women) were included but seven of these were not trials which included women delayed in normal labour but trials of a package of care which included oxytocin called 'active management' of labour (one to one care in labour, strict definition of established labour, early routine amniotomy, routine two hourly vaginal examinations and oxytocin if labour becomes slow). No analysis was presented within the review to differentiate the reason for oxytocin being prescribed. The three trials included in which oxytocin was given for delayed normal labour (similar to the population in our proposed trial) are included in the Cochrane review above.

A recent Swedish trial (Selin et al[10]) which evaluated high versus low dose oxytocin for delay in the first stage of labour recruited 1295 women who were included in an intention-to-treat analysis (high-dose n=647; low-dose n=648). Caesarean section rates did not differ between groups (12.4% and 12.3%, 95% Confidence Interval -3.7 to 3.8). Women with high-dose oxytocin had: shorter labours (-23.4min); more uterine tachysystole (43.2% versus 33.5%); similar rates of instrumental vaginal births, with more due to fetal distress (43.8% versus 22.7%) and fewer due to failure to progress (39.6% versus 58.8%). There were no differences in neonatal outcomes. The trial used similar dose regimens of oxytocin to those proposed in the HOLDS trial, however, women were recruited to the Swedish trial up to four hours earlier in labour than is planned in the HOLDS trial. This means that many, if not most, of the women in the Selin trial were not delayed in labour according to the NICE definition, and the initiation of oxytocin (whether high or low dose) could not be expected to improve outcome, while at the same time risking adverse side-effects. This is supported by the very low rate of caesarean section seen in the Selin trial (12.3% versus the expected 17.5%). The trial also recruited 210 women in the second stage of labour, while these women are not intended to be recruited to the HOLDS trial. In conclusion, this trial did not provide conclusive results applicable to the UK setting.

No other trials are registered on the WHO International Clinical Trials Registry Platform as recruiting women to trials which are exploring the dose of oxytocin for women delayed in the first stage of labour.

Further demonstration of the lack of conclusive evidence regarding routine use of a high dose regimen of oxytocin is seen in the NICE Guidance on Intrapartum Care[5] which did not find sufficient evidence to warrant a review of the recommendation to use the standard dose regimen of oxytocin (2mU/min increasing every 30 minutes to a maximum 32mU/min) for women delayed in labour.

6.2 Additional relevant evidence

In the USA the Consortium of Safe Labor have recently published data that suggests that duration of labour appears longer today than in the past[11] and that a cervical dilation of 6 cm appears to be a better marker for the start of the active phase of labour. This has been adopted by the American College of Obstetricians and Gynecologists with the Society for Maternal-Fetal Medicine in their consensus statement for 'Safe Prevention of Primary Caesarean Section'[12] as part of a number of strategies designed to reduce the caesarean section rate. In this statement they suggest that intervention for delayed labour should not start until the cervix is more than 6cm dilated and it is not clear what the standard oxytocin dose regimen should be. Using the data collected as part of the work undertaken by the Consortium of Safe Labor, an observational study[13] found no difference in CS rates with a so-called high dose oxytocin compared to a low dose. However, this study is open to methodological biases, the exact oxytocin dose regimens are unclear and, as they are presented within the paper, all the regimens would be considered standard dose regimens in the UK. Uptake of this evidence and the Consensus Statement[11] has been controversial in the USA[14] and is unlikely to influence practice in the UK[15]. To ensure that the trial results will be of worldwide interest and relevance we will incorporate subgroup analysis of women commencing treatment less than 6cm and equal to or more than 6cm into our *a priori* statistical analysis plan.

7 Trial aim and objectives

7.1 Internal Pilot Stage Objectives

Criteria for continuation have been based on those proposed by the Internal Pilot Trials Workshop supported by the Hubs for Trials Methodology Research and recently published in British Medical Journal (BMJ) Open[16] Criteria for recruitment, protocol adherence and outcome data as recommended and have included a traffic light system of green (go), amber (amend) and red (stop), detailed in *Table 1* below. Failure to make two-thirds of our recruitment target will be considered as criteria for failure of the internal pilot phase and will be cause to reconsider the transition to the main trial. The Trial Steering Committee will meet to assess these criteria and report their recommendations to the NIHR Health Technology Assessment (HTA). The pilot phase is planned to last 7 months following a nine month set up period.

Table 1: Criteria for continuation to main trial at the end of the internal pilot

	Red (discuss with TSC and consider stopping trial)	**Amber (discuss with TSC strategies for improvement and changes to processes and consider stopping the trial)**	**Green (discuss with TSC strategies for improvement and changes to processes and consider continuation)**	**Actual target (Recruitment projection)** **Above 95% unconditional continuation**
Recruitment				
Sites open	13 <67% of actual	13-17 67-85% of actual	>17 85% of actual	20

	Red (discuss with TSC and consider stopping trial)	Amber (discuss with TSC strategies for improvement and changes to processes and consider stopping the trial)	Green (discuss with TSC strategies for improvement and changes to processes and consider continuation)	Actual target (Recruitment projection) Above 95% unconditional continuation
Total number of participants recruited	<268 <67% of actual	268-340 67-85% of actual	340 85% of actual	400
Protocol adherence				
Proportion receiving allocated treatment	<80%	80-90%	90+%	
Average rate of administration of oxytocin in high dose compared to low dose	<20% increase	20-40% increase	>40% increase	>50% increase[1]
Outcome data				
Proportion primary outcome collected	<80%	80-90%	90+%	

[1]Example for >50% increase: at least 15 mU/min in the high dose group compared with 10 mU/min in the low dose group. A target proportional increase is proposed as we cannot be certain what the average control group rate will be.

7.2 Main trial objectives

HOLDS will provide robust evidence of clinical effectiveness of a high dose compared to the current standard dose regimen of oxytocin in reducing the need for Caesarean section (CS) for nulliparous women with confirmed delay in the first stage of labour.

7.3 Primary objective

- To perform a robust multicentre, randomised, double blind controlled trial to evaluate the effect on CS rate of high dose regimen versus standard dose regimen oxytocin for nulliparous women at term (gestation of 37+0 - 41+6) with confirmed delay in the first stage of labour using NICE definitions.

7.4 Secondary objectives

- To assess the effect on maternal and neonatal outcomes.
- To explore any variation in effect in women randomised with cervical dilation <6cm and >=6cm.
- To assess the safety of high dose oxytocin. Oxytocin can cause excess contractions (tachysystole) which can lead to abnormalities of the fetal heart rate (hyperstimulation) and we will collect information regarding safety for both women and babies.

8 Trial design

8.1 Design

Multicentre, pragmatic, randomised, double blind controlled trial.

8.2 Setting

Delivery Suite of approximately 30 Maternity Units within the UK.

8.3 Inclusion criteria

- Nulliparous women in established spontaneous labour* i.e. no previous births ≥24+0/40:
    - Who have a singleton cephalic pregnancy
    - Gestation of 37 weeks +0 days – 41 weeks +6 days
    - With ruptured membranes
    - For whom the clinical decision has been made to prescribe oxytocin for augmentation of labour, taking the woman's individual circumstances into account**
    - Who give written informed consent to participate prior to randomisation
    - Aged 16 years or above

*For all women labour is established when there are regular painful contractions and progressive cervical dilation from 4 cm. (NICE 2014).
** Delay is suspected when cervical dilation of < 2 cm in 4 hours occurs. Oxytocin may be prescribed either at this stage or when delay is confirmed (when progress of <1 cm in 2 hours is found on repeat vaginal examination).

- COVID-19 positive participants are eligible for study inclusion in accordance with local Trust/Health Board policy.

8.4 Exclusion criteria

- Nulliparous women who:
    - Have reached full dilation of the cervix (10cm)
    - Are undergoing induction of labour
    - Have a BMI >40 at booking
    - Have a multiple pregnancy
    - Have existing:
        - Cardiac disease
        - Bleeding disorders
        - Diabetes (either pre-existing or gestational)
        - Previous uterine surgery
    - Have had significant antepartum haemorrhage
    - Have a known contra-indication to oxytocin therapy as listed in the Summary of marketing Product Characteristics (SPC) and in *Section 9.2* of the protocol)
    - Are participating in other interventional trials of an Investigational Medicinal Product (IMP) or procedure for delay in labour.

8.5 Identifying potential participants

Women are only eligible for the trial if they become delayed in labour. Therefore, in the first instance, arrangements will be made for all nulliparous women to receive written information about the trial during the antenatal period, ideally at about 34 – 36 weeks. This will be in the form of a letter introducing the trial and will include a Participant Information Leaflet. It is the responsibility of individual sites to distribute these letters to potentially eligible women. This will facilitate a discussion about the trial at the visit with the midwife at 35-37 weeks.

This will be organised by the participating sites, through the Research and Development Departments to suit their local practices, but will most likely be sent by the Research Midwife. If a woman decides before labour she does not wish to take part, this will be recorded in her maternity notes and she will not be approached in labour. All women will have the opportunity to ask questions about the trial and to have their questions answered.

8.6 Obtaining informed consent

When a nulliparous woman is admitted to the labour ward potential inclusion will be checked by the midwife responsible for her care, with final eligibility determined by an obstetrician. If appropriate the trial will be discussed as her labour progresses, but raising the possibility of abnormal labour with women who are labouring normally may not be appropriate.

In line with NICE guidance once a woman is in established labour (i.e. she has regular painful contractions and her cervix is 4cm or more dilated on examination) assessment of progress includes cervical dilation as well as descent and rotation of the baby's head and changes in the strength, duration and frequency of uterine contractions. Should delay be suspected (when cervical dilation of <2cm in four hours is found) the woman remains under the care of a midwife. During the period until progress is re-assessed the midwife is likely to suggest interventions which would facilitate progress occurring. This may include encouraging the woman to mobilise, consider hydration (e.g. a sports drink), and discussing appropriate and effective pain relief. If her membranes are still intact, artificial rupture (amniotomy) will also be advised. It is during this window that the HOLDS trial would be discussed and so the midwives role in introducing the trial and answering any questions she may have is vital.

Once delay is confirmed transfer to obstetric-led care would take place (if required) for an obstetric review and a decision about management, including the use of oxytocin. There are some situations when waiting another 2 hours is not appropriate for example if there are few uterine contractions. The clinical team will discuss these individual circumstances and may recommend treatment starts sooner. The midwives' role is fundamental in ascertaining if the woman is potentially eligible, explaining the trial, answering any questions she may have and in providing continuous support. It is at this point trial eligibility would be confirmed by a HOLDS trained Obstetrician and the woman would be consented to trial participation.

It is acknowledged that if the woman, for whatever reason, is not able to give informed consent, recruitment is not appropriate. It may not be suitable for women in labour to be provided with lengthy information and so a summary of the trial will also be provided. After birth, information about the trial will continue to be given as and when requested.

After randomisation, the original completed Informed Consent Form should be filed in in the Investigator Site File, one copy should be given to the participant, one copy should be filed in the medical notes and a further copy should be returned to the HOLDS Trial Office at the BCTU for in-house review.

Training of the clinical staff potentially involved in recruiting or caring for women will depend on the tasks they will undertake. Once recruited, clinical staff will then continue to manage the woman as care is no different to normal practice. The administration of IMP, and clinical care would normally be undertaken by such clinical midwives and therefore falls within their normal sphere of clinical practice. Therefore, the dispensing of the oxytocin can be recorded in the trial Drug Accountability Log which will be kept with the IMP, for recording by the midwife responsible for the woman's care and not necessarily by an obstetrician. The only difference is the strength of oxytocin and allocation is double blinded to participants, clinicians and the research team.

The qualitative work undertaken in the pilot study indicates that the recruitment processes and information provided are acceptable to women[1]. Information regarding the study is given to potentially eligible women during the late antenatal period, with access to more detailed information (by request). As described previously, discussion of the trial begins when delay is suspected but consent can only be obtained once delay in labour is confirmed. The time-window for treatment to be started is relatively short as it is between diagnosis of delay and commencement of the oxytocin (which is the recommended treatment).

8.7 Informing the participants GP

Following the participant giving consent, her GP will be notified using the trial template 'Letter to GP', and a copy kept in the site file.

8.8 Co-enrolment

Women participating in the HOLDS trial cannot join other interventional trials of an IMP or procedure for delay in labour. Women may be recruited to non-interventional trials such as observational or qualitative studies for delay in labour and to all other trials in pregnancy or the postnatal period. Where necessary a sponsor to sponsor agreement will be put in place and sites will be informed accordingly.

8.9 Randomisation

Randomisation will be by telephone via an automated secure system developed by the Centre for Healthcare Randomised Trials (CHaRT) within the Health Services Research Unit at Aberdeen University. Eligibility will be confirmed as part of the recruitment process and checked by the automated telephone randomisation system.

Randomisation will be available 24 hours a day. Participants will be randomised at the level of the individual in a 1:1 ratio to either standard dose regimen oxytocin or high dose regimen oxytocin. A minimisation algorithm will be used to ensure balance in the allocation over the following variables:

- degree of cervical dilation in cm (<6/>=6);
- age in years (<20/>=20 to <30/>=30 to <40/>=40);
- maternity unit

A 'random element' will be included in the minimisation algorithm so that each participant has a probability (unspecified here) of being randomised to the opposite treatment that they would have otherwise received.

Resupply of subsequent treatments, should they be required, will be by the same secure system to guarantee allocation to the same dose as initial randomisation.

9 Trial Treatment/Intervention

9.1 Treatment allocation

The trial will compare the standard dose regimen of oxytocin with a high dose regimen. NICE guidance recommends a standard dose regimen of oxytocin (2mU/min increasing every 30 minutes to a maximum 32mU/min). The comparator is high dose regimen (4mU/min increasing every 30 minutes to a maximum of 64mU/min). The high dose regimen (i.e. double the concentration) has a higher starting dose, earlier attainment of conventional maximum doses (at 2 hours rather than over 4 hours) and the possible use of higher maximum doses of oxytocin compared to the standard regimen.

Women randomised to the standard dose will receive 2 x 5iu ampoules added to diluent (sodium chloride 0.9% or appropriate alternative) to make up a total solution volume of 50mls or 500mls, and those randomised to the high dose will receive 2 x 10iu ampoules added to diluent (sodium chloride 0.9% or appropriate alternative) to make up a total solution volume of 50 mls or 500mls (see *Table 2*: Regimens proposed by HOLDS). The total volume of both oxytocin ampoules is 2ml, therefore it may be necessary to withdraw 2ml of diluent before adding the oxytocin ampoules, to ensure the total solution volume is 50ml or 500ml.

Ampoules are manufactured as 5iu and 10iu and these regimens have been selected to enable the trial to be double-blinded. It is cheap and licensed for this specific use in pregnancy - we intend to use it marginally outside the recommended maximum dose (shaded area in *Table 2*). Synthetic oxytocin is manufactured by Mylan and called oxytocin. The drug is prepared for trial use by Sharp Clinical Services, who blind, label, package and distribute the treatment packs in temperatures compliant with the SPC (between 2-8 ^{o}C). Ampoules are only manufactured in 5 and 10iu and treatment packs contain 2 ampoules and will be stored in a fridge on Delivery Suite. Once made up the expiry time for the infusion is 24 hours.

Collaborating units will be required to submit a Temperature Monitoring Log at least monthly, detailing the daily temperature recordings of the fridge on Delivery Suite that the IMP is stored in - this will be done by the unit electronically into a system which recognises deviations. IMP moved from the Labour Ward to Pharmacy, or removed from the fridge for more than 10 minutes should also be recorded on the log. Where temperatures are above 8 ^{o}C and below 30 ^{o}C (minor temperature deviation) the shelf life of the IMP will be limited to 3 months (in line with SPC). If a minor temperature deviation has been recorded on the paper log, or the minimum and maximum temperature has not been recorded for a given day, sites should enter that month's data up to and including the date of the deviation/missing data and inform the HOLDS Trial Office so that instructions can be sent to the responsible Pharmacist to relabel the affected treatment packs with the reduced expiry date in accordance with local practice. Further details are given in the HOLDS IMP Manual.

The buffered thermometers are supplied to sites by the HOLDS Trial Office for use in the study. The buffered thermometers will alarm if there is a major temperature deviation and the temperature is recorded $< 2^{o}$ or $\geq 30^{0}$C (where there is no stability data). Should this occur, the site must phone the 24/7 telephone randomisation system to halt recruitment at their site, quarantine the IMP and await further instructions from BCTU.

The IMP will have a rolling three monthly expiry date which will only be extended for another three months if there is supporting evidence from the submitted temperature logs that no temperature deviations have occurred. Missing temperature recordings will be treated as a minor temperature deviation. If a temperature deviation has occurred the automated pack management system will ensure that treatment packs requiring destruction are removed from the randomisation system at the appropriate time. It will also support the replacement and destruction of those treatment packs in the collaborating units.

Temperature deviations are expected and in the case of a major temperature deviation this will mean that the trial is suspended temporarily at the site involved. Guidelines for IMP management are outlined in the HOLDS IMP Manual.

A record will be kept of trial drugs dispensed. A trial-specific, Drug Accountability Log is provided to record the date and trial number against the treatment pack. An Obstetrician will prescribe the IMP as 'Oxytocin for HOLDS study' on the participant prescription chart or use the provided HOLDS prescription label which will need to be completed. This will be contained in the HOLDS Labour Pack.

The table below details the regimens proposed by HOLDS. Doses in the shaded boxes are those outside the national recommended regimen.

Table 2: Regimens proposed by HOLDS

	Infusion rate (mls per hour)		Dose of oxytocin (mU/min)	
Time after starting (mins)	*A. With dilution to **50 ml** total volume*	*B. With dilution to **500 ml** total volume*	Standard strength 10 iu in 50mls (total volume)	High strength 20iu in 50mls(total volume)
0	0.6	6	2	4
30	1.2	12	4	8
60	2.4	25	8	16
90	3.6	36	12	24
120	4.8	48	16	32
150	6.0	60	20	40
180	7.2	72	24	48
210	8.4	84	28	56
240	9.6	96	32	64

9.2 Drug Interaction or Contraindications

Contraindications

- Oxytocin is being used in line with the standard clinical care pathway for induction of labour, where oxytocin is indicated. Considerations to the list below should be given as oxytocin is contraindicated in the following situations (list taken from Mylan Syntocinon SPC dated 18th March 2021*):

- Any condition in which, for fetal or maternal reasons, spontaneous labour is inadvisable and/or vaginal delivery is contra-indicated: e.g.:
    - Significant cephalopelvic disproportion
    - Fetal malpresentation
    - Placenta praevia and vasa praevia
    - Placental abruption
    - Cord presentation or prolapse
    - Overdistension or impaired resistance of the uterus to rupture as in multiple pregnancy
    - Polyhydramnios
    - Grand multiparity.
- In the presence of a uterine scar as a result of major surgery.
- Oxytocin should not be used for prolonged periods in patients with oxytocin-resistant uterine inertia, severe pre-eclamptic toxaemia or severe cardiovascular disorders.

Within the parameters of the trial, consideration towards contraindications will be managed as per the standard of care for each participating hospital site.

*Please refer to the current SPC for the most up to date contraindications.

Drug Interactions

Concomitant medication not recommended

Oxytocin is not recommended for concomitant use with the following therapeutics:

Drugs prolonging the QT interval

Oxytocin should be considered as potentially arrhythmogenic, particularly in patients with other risk factors for Torsades de Pointes such as drugs which prolong the QT interval or in patients with history of long QT syndrome.

Concomitant medication to be used with caution

When using oxytocin the following interactions are to be considered:

Inhalation anaesthetics

Inhalation anaesthetics (e.g. cyclopropane, halothane, sevoflurane, desflurane) have a relaxing effect on the uterus and produce a notable inhibition of uterine tone and thereby, may diminish the uterotonic effect of oxytocin. Their concurrent use with oxytocin has also been reported to cause cardiac rhythm disturbances.

Vasoconstrictors/Sympathomimetics

Oxytocin may enhance the vasopressor effects of vasoconstrictors and sympathomimetics, even those contained in local anaesthetics.

Caudal anaesthetics

When given during or after caudal block anaesthesia, oxytocin may potentiate the pressor effect of sympathomimetic vasoconstrictor agents.

There are no restrictions on breastfeeding for women recruited to the HOLDS trial.

9.3 Treatment modification

The dose of oxytocin is titrated against uterine activity and the fetal heart rate, so it may be temporarily stopped and re-started and this does not mean the participant would be withdrawn or that there is a protocol deviation. No other treatment modifications can be considered by clinical staff.

9.4 Cessation of treatment / continuation after the trial

If a woman decides, after randomisation, she does not wish to be part of the trial she will be withdrawn from the trial and will receive the standard dose oxytocin regimen using non-trial treatment. The timing of randomisation is as close as possible to the commencement of treatment so this should minimise the number of post-randomisation withdrawals. Participants may cease to participate in a particular aspect of the trial and these participants will be considered as changing their status in the trial (see *Section 9.7* for further details). Oxytocin is given during labour and is not continued afterwards.

9.5 Care of women following randomisation until birth

Delay in labour is an everyday occurrence on UK Delivery Suites and intravenous infusion of oxytocin has been the treatment employed since the 1960s. It is licensed for this specific indication. The dose is titrated against the strength and frequency of uterine contractions, taking into account fetal wellbeing using cardiotocograph monitoring (fetal heart rate patterns), with the desired outcomes being re-establishment of effective uterine contractions, dilation of the cervix and vaginal birth. Obstetricians and midwives are used to managing women receiving intravenous oxytocin so, although the randomised design is double blinded, the clinical team on duty are very unlikely to encounter unfamiliar clinical problems.

The safety of mother and baby receiving oxytocin are routinely addressed by more intense monitoring than normal labour by the midwife and obstetrician caring for the woman. Routine care in labour is recommended by NICE Guidance[5] and would normally include one-to-one care from a midwife, support and effective pain relief, frequent monitoring of the strength and frequency of contractions, the observations of the woman's vital signs (hourly pulse and four hourly temperature and blood pressure) and her fluid balance.

Continuous Electronic Fetal Monitoring (CEFM) to detect signs of developing fetal hypoxia is always used in the presence of oxytocin. Non- reassuring or abnormal features of the fetal heart rate pattern would be recorded according to NICE guidance and a fetal blood sample obtained when indicated to assess the fetal condition (current best practice). Usual care is detailed below:

- if the fetal heart rate (FHR) trace is normal, oxytocin may be continued until the woman is experiencing 4 or 5 contractions every 10 minutes. Oxytocin should be reduced if contractions occur more frequently than 5 contractions in 10 minutes
- if the FHR trace is classified as non- reassuring , an obstetrician should be informed
- if the FHR trace is classified as abnormal , this should be reviewed by an obstetrician.

Should either uterine tachysytole (defined as more than 5 contractions in 10 minutes for 20 minutes or more with a normal fetal heart rate) or uterine hyperstimulation occur (defined as tachysystole with non-reassuring or abnormal fetal heart rate) this will be documented and obstetric opinion sought. In these situations oxytocin would be reduced, stopped or tocolysis commenced as is usual practice. The rate of reduction of oxytocin, should that be required for any reason, will depend on clinical circumstance and should follow normal clinical practice.

Following commencement of oxytocin current NICE guidance advises the woman to have a vaginal examination 4 hours later (unless otherwise indicated). If cervical dilatation has increased by less than 2 cm after 4 hours of oxytocin, further obstetric review is required to assess the need for Caesarean section. If cervical dilatation has increased by 2 cm or more, labour is allowed to progress with vaginal examinations as per local routine practice.

The care pathways for the women are identical regardless of the randomly allocated dose regimen of oxytocin; the only difference is the concentration of the oxytocin they receive. Participating in the study will not alter the care the woman or baby receives should any anticipated or unanticipated problem occur, and standard procedures, as defined within the local Maternity Unit protocols, would then be followed.

9.6 Unblinding of trial participants

Unblinding of participants as an emergency will not be necessary as the management of the women will not change in the light of this information. Any adverse event that occurs from whichever trial treatment the woman is randomised to should be managed by the clinical team caring for the woman as per local protocols. The plasma half-life of oxytocin is approximately five minutes, so should any cause for concern be identified, stopping the oxytocin is the most common and effective treatment.

However, should this be required as part of any investigation, access to unblinded treatment will be through the trial office who will be able to unblind during normal working hours. . Reasons for unblinding will be documented.

9.7 Withdrawal of trial/treatment and change of status within the trial

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation.

Participants should be aware at the beginning that they can freely withdraw (discontinue participation) from the trial at any time. A participant who withdraws from the trial does so completely (i.e. from trial treatment and all follow up) and is not willing to have any further data collected. A participant who wishes to cease to participate in a particular aspect of the trial, will be considered as having changed their status within the trial.

The Participant Information Leaflet states that if a participant does not receive trial treatment or chooses to discontinue trial treatment early, their data (birth and discharge outcome data) will still be collected and reported to the HOLDS Trial Office, unless they explicitly state their intention to withdraw from all aspects of the trial to the local Research Team.

The details of either withdrawal or change of status within the trial (date, reason and if consent is withdrawn to continued data collection) should be clearly documented in the source documents and recorded on the Birth and Discharge Form. Participants subsequently found to be ineligible will still have their data analysed unless they explicitly withdraw consent.

Should a woman lose capacity to provide continued consent, it will be assumed that they wish to remain in the HOLDS trial as there would be no further procedures or tests required for the trial.

10 Outcome measures

10.1 Primary Outcome

- Caesarean Section (CS)

10.2 Secondary maternal outcomes

Clinical outcomes

- Epidural use during labour
- Duration of first, second and third stages of labour
- Time to birth from randomisation
- Mode of birth (spontaneous vaginal birth (SVB), instrumental or CS)
- Degree of perineal trauma (first, second, third and fourth degree)
- Reason for CS and decision to delivery interval for CS
- Confirmed urinary retention requiring catheterisation and pulmonary oedema
- Tachysystole (uterine contractions greater than 5 in 10 mins for 20 minutes) requiring reduction in oxytocin and/or tocolysis
- Hyperstimulation (uterine contractions greater than 5 in 10 mins for 20 minutes resulting in non- reassuring or abnormal fetal heart rate)
- Fetal blood sampling (FBS) during labour or significant STAN event (for those Units that use ST waveform analysis for intrapartum fetal monitoring)
- Abnormal cardiotocogram leading to immediate birth without fetal blood sample
- Incidence of possible maternal morbidity (anaphylaxis, pulmonary oedema, postpartum haemorrhage, shoulder dystocia, chorioamnioitis, uterine rupture/hysterectomy)
- Active management of third stage of labour
- Length of time after birth in hospital [days]
- Admission to HDU/ITU
- Maternal death

Process outcomes

- Time from randomisation to commencement of allocation
- Total oxytocin dose
- Time to maximum oxytocin rate
- Maximum oxytocin dose reached

10.3 Neonatal secondary outcomes:

- Gender and birthweight
- Apgar score at 5 minutes
- Arterial and venous cord blood gases when collected
- Breastfeeding rates on discharge from hospital
- Length of time after birth in hospital [days]
- Resuscitation
- Reason for neonatal review on ward (excluding routine baby check)
- Reason for admission to neonatal unit (NNU) and level of care received (level 1,2,3) including intensive care
- Duration of respiratory support
- Days to full suck feeds

- Seizures
- Neonatal encephalopathy (SARNAT grade)
- Therapeutic hypothermia (cooling) if required
- Intrapartum still birth
- Early neonatal death (within seven days of birth)

11 Adverse Event Reporting

The collection and reporting of Adverse Events (AEs) will be in accordance with the UK Policy Framework for Health and Social Care, and the Medicines for Human Use Clinical Trials Regulations 2004 (and its subsequent amendments).

It is the responsibility of investigators to notify safety events to the HOLDS trial office who will report these as required. It is therefore imperative that all investigators have a thorough understanding of anticipated serious adverse events and the reporting process of these events.

The investigator should document all AEs experienced by the trial participant in the source data and assess the seriousness and causality (relatedness [serious events only]) with reference to Section 4.8 'Undesirable Effects' of each of the following Summary of Product Characteristics (SPCs):

- Oxytocin 5 IU/ml Concentrate for Solution for Infusion, Mylan
- Oxytocin 10 IU/ml Concentrate for Solution for Infusion, Mylan

Investigators will be provided with a copy of the most recent oxytocin SPCs at site setup and sites will be responsible for ensuring that they are filed in the Investigator Site File (ISF). Any subsequent updates to the SPCs will be provided by the HOLDS Trial Office and should be implemented immediately by the site and filed in the ISF; the previous versions should be marked as superseded.

All events will be documented in the medical notes from randomisation until discharge from hospital.

11.1 General Definitions

Table 3: Adverse Event Definitions

Adverse Events (AEs)	An AE is any unintentional, unfavourable clinical sign or symptom.
Adverse Reactions (ARs)	An AR is an adverse event that is considered to have a "reasonable causal relationship" with any trial drug.
Serious Adverse Reactions (SARs) or Serious Adverse Events (SAEs)	Any AR or AE that: at any dose: • Results in death • Immediately threatens the life of participant* • Results in hospitalisation or a longer than anticipated stay in hospital • Results in a persistent or significant disability or incapacity

	Is otherwise considered medically significant by the Investigator**
Events and Reactions not classed as serious that require reporting	See *Section 10.2*
Suspected unexpected serious adverse reactions (SUSARs)	A SUSAR is an SAE suspected to be related to a product, which is of a type or severity which is NOT consistent with the Summary of Product Characteristics (SPC) for oxytocin.

*Life-threatening in the definition of a serious adverse event refers to an event in which the mother 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. Important adverse events that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the pregnancy or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

** Medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definitions above.

The definition of a SAR or SAE usually includes any congenital anomaly or birth defect in any pregnancy; however, the intervention is given briefly towards the end of labour beyond 37 weeks' gestation where it cannot have any possible teratogenic effect. Any babies with congenital anomalies will not be considered to be a SAR or SAE.

11.2 Adverse Event (AE) Reporting

The following non-serious AEs (and ARs) occurring from the time of trial treatment commencement until birth of the baby should be collected on the Labour Form and reported on the Birth and Discharge Form:

Maternal outcomes

- Headache
- Nausea
- Vomiting
- Tachycardia or bradycardia
- Hyponatraemia

The assessment of severity for AEs and ARs that do not meet the criteria for serious will not be collected due to the well understood safety profile of oxytocin. Assessment of severity of SAEs and SARs will be captured (see *Section 11.5* below).

Labour outcomes

There are a number of expected labour ARs listed in the current oxytocin SPC (at the time of protocol finalisation), which are considered to be of 'not know' frequency (i.e., isolated reports that cannot be estimated from the available data) which include:

- Uterine tachysytole (defined as more than 5 contractions in 10 minutes for 20 minutes or more with a normal fetal heart rate)
- Uterine hyperstimulation (defined as tachysystole with non- reassuring or abnormal features of the fetal heart rate)

Our pilot study found that 17% of the standard dose group (8/47) had an episode of uterine tachysystole with 11% (5/47) experiencing hyperstimulation. With our proposed sample of 1,500 women, we would have 80% power to detect an absolute increase of 6% in the rate of tachysystole (i.e. 17% to 23%) and a 5% increase (i.e. 11% to 16%) for hyperstimulation.

11.3 Serious Adverse Event (SAE) Reporting

SAE (and SAR) reporting by the Investigator will fall into one of the following categories:

Table 4: HOLDS SAE Reporting Requirements

SAE to be reported in an expedited manner	Events that meet the criteria for serious which are not listed in the SAE reporting exemptions should be reported on an **SAE Form** and sent to the BCTU Trials Office within 24 hours of the Research Team becoming aware. See *Section 11.3.1* below for further details.
Expected SAEs for prolonged hospital stays	Events should be documented in the medical notes and do not require reporting to the Trial Office via the SAE Form. See *Section 11.3.2* below for further details.

When an SAE occurs in a different department at the same hospital at which the participant is receiving trial treatment or is being followed up for trial purposes, processes must be in place to ensure the trial team at the hospital are made aware in an expedited manner, regardless of which department first becomes aware of the event.

11.3.1 Events that require expedited reporting to the BCTU

All SAEs (except those listed in *Section 11.3.2*) require expedited reporting from the date of commencement of protocol defined treatment until discharge from hospital. All SAEs should be followed up until stabilisation or resolution of the event.

In addition to the definitions of an SAE and SAR given in *Table 3*, the following events (listed for convenience, but are not limited) should be reported on an **SAE Form**:

Maternal outcomes

- Serious maternal hyponatraemia (symptomatic hyponatraemia [Na <125mmol/l] in labour or in the immediate 48 hours following delivery, not caused by sepsis or pre-eclampsia, where other likely causes have been clinically excluded)Maternal anaphylaxis
- Maternal pulmonary oedema
- Uterine rupture/ hysterectomy
- Postpartum haemorrhage that triggers the Massive Obstetric Haemorrhage protocol, including blood transfusion
- Maternal admission to HDU/ITU- requiring critical care level 2 or 3
- Maternal death*

Neonatal outcomes

- Unexpected provision of neonatal **intensive** care
- Neonatal seizures
- Neonatal encephalopathy*
- The need for neonatal therapeutic hypothermia and
- Intrapartum stillbirth*
- Neonatal death*

*Should a maternal death, intrapartum stillbirth, neonatal death or neonatal encephalopathy be reported, each instance will be reported promptly to the Data Monitoring Committee (DMC) by the BCTU Trials Office.

11.3.2 Events that do not require reporting to the BCTU

The below events should still be recorded in the medical notes, but do not need to be reported on an SAE Form and do not require expedited reporting to the BCTU Trials Office (within 24 hours of the Research Team becoming aware):

These include prolonged hospital stays for the following reasons:

- For baby due to breast feeding issues
- For baby due to jaundice
- For baby due to the administration of IV antibiotics (this includes admission to NNU if the admission is for preparation of IV antibiotics administration i.e. cannula sited and bloods taken only)
- For mother due to the administration of IV antibiotics
- For mother for feeding and emotional support
- Due to recovery from instrumental birth or caesarean section.

11.4 SAE reporting process

11.4.1 Reporting process for SAEs requiring an SAE Form

On becoming aware that a participant has experienced an SAE (or SAR), the Investigator or delegate(s) should report the SAE to the BCTU Trials Office, as well as to their own organisation in accordance with local practice.

To report an SAE to the BCTU Trials Office, the Investigator or delegate(s) must complete, date and sign the HOLDS **SAE Form**. The completed form together with any other relevant, appropriately anonymised, data should be scanned and emailed to the BCTU Trials Office using the email address listed below as soon as possible and no later than 24 hours after first becoming aware of the event.

To report an SAE email the SAE Form to: HOLDS@trials.bham.ac.uk

On receipt of an SAE Form, the BCTU Trials Office will allocate each SAE a unique reference number and return this via email to the site as proof of receipt. In the unlikely event that the site has not received confirmation of receipt of the SAE from the BCTU, or if the SAE has not been assigned a unique SAE identification number within 1 working day, the site should contact the BCTU Trials Office, to ensure receipt of the SAE. The site and the BCTU Trials Office will ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE, and filed with the SAE in the Investigator Site File (ISF) and Trial Master File (TMF).

Where an SAE Form has been completed by someone other than the Investigator or delegate, the original SAE Form will need to be countersigned by the Investigator to confirm agreement with the causality and severity assessments.

11.4.2 Provision of follow up information

Following reporting of an SAE for a participant, the participants should be followed up until resolution or stabilisation of the event. Follow-up information should be provided to the BCTU Trials Office via the **SAE Form** and quoting the SAE reference number provided.

Once the SAE has been resolved, all critical follow-up information has been received and the paperwork is complete, the final version of the original SAE Form completed at site must be returned to the BCTU Trials Office by post and a copy kept in the Investigator Site File.

11.5 Assessment of severity of SAEs

When completing the **SAE Form**, the PI will be asked to define the causality (relatedness) and the severity of the AE. The assessment of severity of SAEs is a clinical decision based on all available information at the time. The following categories will be used to define the severity of the SAE:

Table 5: Categorisation of Severity of SAE Events

Category	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activities of daily living (ADL)**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bed ridden.

11.6 Assessment of relatedness of SAEs

In defining the causality (relatedness) the PI must also consider if any concomitant events or medications may have contributed to the event and, where this is so, these events or medications should be reported on the **SAE Form**. It is not necessary to report concomitant events or medications which do not contribute to the event.

Table 6: Definitions of serious adverse event causality

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.	
Possibly	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events or medication).	
Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant events or medication).	Unrelated
Not related	There is no evidence of any causal relationship.	

The BCTU Trials Office will review all SAE Forms received on receipt to ensure they meet the criteria for reporting, before forwarding it, with the unique reference number, to the Chief Investigator (CI) or delegate(s) and clinical co-applicant who will independently review the seriousness, causality and expectedness of the SAE. An SAE judged by the PI, CI or clinical co-applicant to have a reasonable causal relationship with the intervention will be regarded as a related SAE (SAR) [see *Table 3* for definition).

The causality assessment given by the PI will not be downgraded by the CI or clinical co-applicant. If the CI or clinical co-applicant disagrees with the PI's causality assessment, the opinion of all parties will be documented, and where the event requires further reporting, this will be provided with the report.

11.7 Assessment of Expectedness by the CI and clinical co-applicant

The CI and a relevantly qualified clinical co-applicant will also assess all related SAEs for expectedness with reference to the following criteria:

Table 7: Definitions of serious adverse event expectedness

Category	Definition
Expected	An adverse event that is consistent with known information about the trial related procedures or that is clearly defined in the relevant safety information.
Unexpected	An adverse event that is <u>not</u> consistent with known information about the trial related procedures.

The CI and a relevantly qualified clinical co-applicant may request further information from the clinical team at site which should be made available immediately upon request. The CI or clinical co-applicant will not overrule the severity or causality assessment given by the site Investigator but may add additional comment on these. If the event is serious and related and unexpected (i.e. is not defined in the approved version of the RSI, it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR) and reported as such (see *Section 11.9)*.

11.8 Reporting SAEs to Investigators

Details of all SUSARs and any other serious safety issue which arises during the course of the trial will be reported to PIs. A copy of any such correspondence should be filed in the Investigator Site File.

11.9 Reporting SAEs to third parties

The independent Data Monitoring Committee (DMC) will have the opportunity to review any SAEs at their meetings. Should a maternal death, intrapartum stillbirth, neonatal death or neonatal encephalopathy be reported, each instance will be reported promptly to the DMC.

BCTU will report details of all SARs (including SUSARs) to the Medicines and Healthcare products Regulatory Agency (MHRA), main REC and external Sponsor annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report (DSUR). Additionally, BCTU will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the MHRA, main REC and external Sponsor within 7 days. Detailed follow-up information will be provided within an additional 8 days.

All other events categorised as non-life threatening SUSARs will be reported within 15 days.

The main REC and external Sponsor will be notified immediately if a significant safety issue is identified during the course of the trial.

11.10 Urgent Safety Measures (USM)

If any urgent safety measures are taken, this will be communicated immediately to the MHRA by the Sponsor via a phone call with the MHRA Clinical Trial Unit. The BCTU shall then immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the REC and MHRA of the measures taken and the circumstances giving rise to those measures.

11.11 Safety reporting responsibilities

11.11.1 Local Principal Investigator (or Co-Investigator in PI's absence)

- To record **all** safety events that occur in the women taking part in the trial. This includes serious, expected or unexpected adverse events, unless defined as an event that does not need to be reported, or requires non-expedited reporting to the BCTU (see *Section 11.3.2*)
- Medical judgement in assigning seriousness, causality and relatedness to SAEs
- To send SAE forms to BCTU within 24 hours of becoming aware, and to provide further follow-up information as soon as available
- To report SARs/SAEs to local committees if required, in line with local arrangements
- To sign a Clinical Site Agreement accepting these responsibilities.

11.11.2 Chief Investigator (CI) (or delegate)

- To assign initial causality, seriousness expectedness and relatedness of SAEs where it has not been possible to obtain local assessment
- To review all events assessed as SAEs in the opinion of the local investigator for causality, seriousness, expectedness and relatedness and obtain obstetric/ neonatal co-applicant's review and assessment
- Alert the DMC Chair if concerned.

11.11.3 Birmingham Clinical Trials Unit (BCTU)

- Allocate each SAE form with a unique reference number and update the SAE form (containing the completed unique reference number), returning proof of receipt and the unique reference number to the site within 1 working day
- In event of a SUSAR - report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the MHRA, main REC and the TMG within 7 days and follow up as required
- Notify the MHRA, main REC immediately if a significant safety issue is identified during the course of the trial
- Report details of all SUSARs and any other safety issue which arises during the course of the trial to PIs
- To prepare development safety update reports to the REC and MHRA. These will be submitted by the BCTU following approval from the sponsor
- To prepare SAE safety reports for the DMC following a timetable agreed by the DMC prior to trial commencement, or as requested by the DMC
- To report all fatal SAEs to the DMC for continuous safety review.

11.11.4 Trial Steering Committee (TSC)

- To provide independent supervision of the scientific and ethical conduct of the trial on behalf of the Trial Sponsor and funding bodies
- To review data, protocol deviations, outcome capture rates, adverse events (during treatment and up to the end of follow-up)
- To receive and consider any recommendations from the DMC on protocol modifications.

11.11.5 Data Monitoring Committee (DMC)

- To review (initially at approximately six-monthly intervals) overall safety and morbidity data to identify safety issues which may not be apparent on an individual case basis
- To recommend to the TSC whether the trial should continue unchanged, continue with protocol modifications, or stop in view of trial safety information
- Promptly review reports of maternal deaths, intrapartum stillbirths, neonatal deaths or neonatal encephalopathy provided by the BCTU.

11.11.6 Sponsor

- To ensure safety reports and delegated duties are completed by key individuals
- Review SAEs and SUSARS
- Ensure safety reports/issues are reported appropriately
- Ensure compliance with regulatory approvals and legislation
- Maintain oversight of safety issues throughout trial.

12 Data Management

12.1 Data collection forms

Data for the purpose of assessing the efficacy and safety within the HOLDS trial will be collected from the participating maternity units by the clinical team responsible for the women's care on a number of data collection (case report) forms (CRFs).

Data required for the primary and the majority of secondary outcomes are objective measures which are routinely collected for clinical purposes and will be transcribed from the woman's medical records, with the exceptions of the amount of oxytocin infused during labour, episodes of tachysystole and hyperstimulation and action taken, grade of obstetrician, highest oxytocin rate infused and pharmacovigilance information which will be directly recorded onto the Labour Form. The respective data from the woman's medical notes and Labour Form constitute source data.

Paper forms will be used to confirm eligibility (prior to telephone randomisation), to document informed consent and to collect data during labour. Information from the CRFs and outcome data will be entered onto the database by those with on-line access. It can be completed in paper form in the first instance but needs to be entered into the secure online HOLDS database by the designated HOLDS midwife (or other personnel delegated this duty on the Site Signature and Delegation Log) in a timely manner – ideally within five days of the woman's discharge. The original Trial Entry Form should be returned by post to the HOLDS Trial Office and a copy retained at sites. All other paper CRFs should be filed with the Trial Entry Form copy and the Informed Consent Form in the Investigator Site File.

The Trial Office will only use a unique identifier for the participant for the purpose of data management.

The clinical personnel involved will be allocated personal usernames and passwords that will only allow access to forms for the trial participants who are being treated at their site. Data validation is built into the online database and additional validation checks will be carried out by the BCTU. Range, date and logic checks are performed at the point of data entry. Email reminders will be sent to the research midwives by the HOLDs Trial office, for missing data forms, missing data or data inconsistencies. This will be followed by phone contact. The expectation is that missing data forms and queries should be completed by the site within 30 days of receipt and should this not occur, will be expedited to the PI.

Table 8: Case Report Form schedule

Form Name	**Schedule for submission**
Informed Consent Form	Collected prior to or at the point of randomisation or earlier as described in S*ection 8.5 Identifying potential participants.* Copy to be sent to the HOLDS Trial Office by post or secure email following randomisation with the patient's explicit consent (see S*ection 8.6 Obtaining informed consent*)
Trial Entry Form	Confirmation of eligibility by a targeted HOLDS trained obstetrician and via the automated telephone randomisation service Original Trial Entry Form to be returned by post to the HOLDS Trial Office as soon as possible
Birth and Discharge Form	Returned to the HOLDS Trial Office electronically within 5-10 days of randomisation-
Neonatal Form	Completed only for those babies who are admitted to NNU

Form Name	Schedule for submission
	Returned to the HOLDS Trial Office electronically within 5-10 days of the end of the care episode
Serious Adverse Event Form	Completed and emailed to the HOLDS Trial Office within 24hrs of research staff at site becoming aware of event Original SAE Form to be returned by post to the Trial Office within 5-10 days of event reporting

Data reported on each form will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Protocol and GCP non-compliances should be reported on a Deviation Form to the Trial Office on discovery.

In all cases it remains the responsibility of the site's PI to ensure that the CRF has been completed correctly and that the data are accurate. This will be evidenced by the signature of the site's PI on the eCRF or paper CRF where appropriate (e.g. the SAE Form).

12.2 Summary of data collection points, personnel and training requirements

All Clinicians will receive targeted HOLDS training which includes relevant elements of GCP training, the study protocol and safety reporting to enable them to introduce the study to potential participants, answer any questions, take informed consent, randomise the woman and dispense the CTIMP. It has been developed and agreed in collaboration with NIHR GCP Trainers. The Obstetrician confirming eligibility and prescribing the CTIMP requires the same targeted HOLDS training.

Full GCP training for the PI and Research Midwife is expected to be that provided by the NIHR. If alternative GCP training has been undertaken content must be reviewed by the BCTU Trial Office and Sponsor to ensure it is acceptable.

Table 9: Personnel and training requirements

Process	Time	CRF	Person responsible
Approach potentially eligible women	When delay is suspected	None	HOLDS trained Obstetrician or Midwife
Eligibility	When delay confirmed	Trial Entry Form	HOLDS trained Obstetrician
Consent	Following confirmation of eligibility	Informed Consent Form	HOLDS trained Obstetrician or Midwife
Randomisation telephone call	Following confirmation of consent	Complete Trial Entry Form	HOLDS trained Obstetrician or Midwife
Prescription of drug	Following randomisation	Prescription chart	HOLDS trained Obstetrician
Study treatment administration	Following prescription of drug	Labour Form	HOLDS trained Midwife or Obstetrician

Process	Time	CRF	Person responsible
Labour data collection	From commencement of study treatment until after birth	Labour Form	HOLDS trained Midwife
Birth outcome data collection	After discharge	Birth and Discharge Form	Site HOLDS Midwife
SAE reporting Determination of Causality of SAE	When they occur	SAE Form	Site HOLDS Midwife Site PI (or medically qualified delegate)

12.3 Definition of the End of Trial

The trial will be deemed complete when the last recruited woman has given birth and outcome data collected and entered onto the data collection system.

For participants the End of Trial is end of discharge from maternity unit or death for the mother, and discharge from maternity or neonatal unit or death with 7 days for the baby.

13 Statistical methods and analysis

13.1 Sample size

The sample size is informed by the pilot study[1], recent survey of practice and Cochrane review[6]. The pilot study indicated a CS rate of 32% in the standard dose group (95%CI: 19% to 45%), whilst responses from the survey of practice (n=60 responses) indicate that a 25% relative reduction would be considered an important clinical difference to change practice. Detecting a difference of this size assuming a standard dose group rate of 32% (8% absolute reduction down to 24%) with 90% power (p=0.05) will require 1320 women. If the control group rate is lower, e.g. 24%, recruiting 1500 women would give 80% power to detect the same relative difference. We have selected the latter figure as our target sample size. The independent Data Monitoring Committee (DMC) will review the event rate to monitor the control rate on a six-monthly basis throughout the recruitment period.

13.2 Statistical analysis

A separate Statistical Analysis Plan will provide a detailed description of the planned analyses. A brief outline is given below.

Point estimates and two-sided 95% confidence intervals will be calculated for all main outcome measures. P-values will be reported from two-sided tests at the 5% significance level for the primary outcome and Serious Adverse Events only. All estimates will be adjusted for the minimisation variables (degree of dilation at recruitment, age and maternity unit) in the regression models where possible. Analysis will be of all randomised subjects in the intention to treat population.

13.2.1 Primary Outcome Analysis

The primary endpoint is the effect on CS rate of high does regimen versus standard dose regimen oxytocin. A log-binomial regression model will be used to calculate the relative risk and 95% confidence interval. The p-value from the associated chi-squared test will be produced and used to determine statistical significance.

13.2.2 Secondary Outcome Analysis

Dichotomous secondary outcomes (e.g. vaginal birth, tachysystole) will be analysed in the same fashion as the primary outcome. Time from randomisation to birth will be analysed by log-rank test with a Cox Proportional Hazard (PH) model also built if the assumptions of proportionality are met. Standard methods will be used to analyse other outcomes. Appropriate summary statistics split by group will be presented for each outcome (e.g. proportions/percentages, mean/standard deviation or median/interquartile range).

13.2.3 Missing Data/Sensitivity Analyses

Every attempt will be made to collect full follow-up data on all women (unless a woman withdraws consent for follow-up data collection). In particular, participants will continue to be followed-up even after any protocol treatment deviation or violation. It is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis. This presents a risk of bias, and secondary sensitivity analyses will be undertaken to assess the possible impact of the risk. This will include a worse-case assumption that those women missing the primary outcome had a caesarean section. Other sensitivity analyses will involve simulating missing responses using a multiple imputation (MI) approach.

13.2.4 Subgroup Analyses

Subgroup analyses will be limited to degree of cervical dilation at recruitment (<=6m/>6cm) in the primary outcome only. Tests for statistical heterogeneity will be performed through examination of the relevant interaction parameter in the regression model.

13.2.5 Interim Analyses

Interim analyses will be conducted on behalf of the DMC. These will be considered together with a full safety report including Serious Adverse Events. The DMC will meet before recruitment commences, and thereafter at least annually. Effectiveness and futility criteria will be ratified by the DMC; suggested stopping criteria are based on a pragmatic approach with further details given in section regarding the DMC. The DMC Charter will include a specific remit for reviewing emerging data from other trials.

13.2.6 Final Analysis

The primary analysis for the study will occur after all randomised women have completed full follow-up and outcome data has been entered into the study database.

14 Data access and quality assurance

14.1 Risk assessment

The Sponsor has performed a risk assessment of the trial prior to commencement that will be reviewed at regular intervals during the course of the trial. This is a trial involving a medicinal product licensed in the UK related to the licensed range of indications, dosage and form; it is proposed that the trial be considered to be of Type A (risk no higher than that of normal clinical practice).

14.2 Ethical considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/).

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research 2017, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and the General Data Protection Regulation (GDPR) 2018. This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations. The protocol will be submitted to and approved by the main REC prior to circulation and the start of the trial. All correspondence with the MHRA and/or REC will be retained in the Trial Master File and Investigator Site File, and an annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given by the REC, and annually until the trial is declared ended.

Before any participants are enrolled into the trial, the PI at each site is required to provide confirmation of capacity and capability. Sites will not be permitted to enrol participants until written confirmation of capacity and capability is received by the HOLDS Trials Team, site initiation training is complete and the HOLDS Trial Office gives the green light for site activation to recruitment.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual Clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

14.3 Confidentiality of personal data

Women will be identified using only their unique trial number and initials to verify identify on the data collection forms and in any correspondence between the HOLDS Trial Office and the participating site.

Collaborating sites will store original consent, a copy of the Trial Entry Form and all paper data collection forms securely in the Investigator Site File (ISF). These forms will be available to various regulatory bodies for inspection upon request. A copy of the consent form (with the women's name) will be posted to the HOLDS trial office at the BCTU where it will be stored separately to the trial record and other participant data. The University of Aberdeen collects the participant's date of birth as part of the telephone randomisation process and this data is entered on to the secure online data entry system at site.

Data collected will be entered onto a secure computer database, directly by the local site *via* the internet using secure socket layer (SSL) encryption technology. Access control will ensure that local trials staff will only be able to view information relating to participants at their site.

All staff involved in the HOLDS trial, be they clinical, academic, or employees of BCTU, share the same duty of care to prevent unauthorised disclosure of personal information. No data that could be used to identify an individual will be published. Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 1998 and any amendments.

14.4 Quality Assurance

14.4.1 Monitoring and Audit

This trial will be regularly monitored by the sponsor to ensure compliance with GCP, in accordance with the monitoring plan developed by the sponsor. A risk proportionate approach to the initiation, management and monitoring of the trial will be adopted and outlined in the trial-specific risk assessment. The sponsor will undertake a risk assessment prior to the trial commencing, which will be regularly reviewed based on trial progress, and monitoring findings which will include poor data quality, excessive number of deviations. All sites will be informed of monitoring visits in advance. In addition BCTU will undertake remote monitoring as part of their quality assurance checks, this will include staff checking incoming informed consent forms and eCRF's. Sites will be sent data clarification forms requesting missing data or clarification of inconsistencies and discrepancies.

14.4.2 Direct Access to Source Data

Investigators and their host Trusts will be required to permit trial-related monitoring and audits to take place by the HOLDS Trial Manager and sponsor representative, providing direct access to source data and documents as requested. The trial site may also be subject to audit by the Research and Development Office of their own Trust, or additional monitoring by the sponsor, and should do everything requested by the Chief Investigator in order to prepare, contribute and provide follow-up to any inspection or audit. Sites are also requested to notify BCTU of any relevant inspections. Trial participants will be made aware of the possibility of external audit of data they provide in the participant information leaflet (PIL).

14.4.3 Definition of a serious breach

A serious breach is that which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the participants of the trial; or
- The scientific value of the trial.

If a potential serious breach is identified by the Sponsor, Chief investigator, Principal Investigator or BCTU, the HOLDS Trial Office must be notified within 24 hours. It is the responsibility of the Chief Investigator and the sponsor to determine whether the incident constitutes a serious breach and if so, to assess the impact of the breach on the scientific value of the trial or the safety of participants. In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments, the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial, within 7 days of becoming aware of that breach. This includes reporting serious breaches of GCP and/or the trial protocol to the REC and MHRA.

14.5 Trial Steering Committee

The Trial Steering Committee (TSC) provides independent supervision for the trial, providing advice to the Chief and Co- Investigators and the sponsor on all aspects of the trial and affording protection for participants by ensuring the trial is conducted according to the guidelines for Good Clinical Practice.

If the Chief and Co-Investigators are unable to resolve any concern satisfactorily, Principal Investigators, and all others associated with the trial may write, through the Trial Office, to the chairman of the TSC drawing attention to any concerns they may have about the possibility of particular side-effects, of particular categories of participant requiring special trial, or any other matters thought relevant.

14.6 Data Monitoring Committee

If the high dose regimen differs from standard dose with respect to the primary or major secondary outcome, then this may become apparent before the target recruitment has been reached. Similarly, new evidence might emerge from other sources that high dose differs in its effectiveness compared with standard dose. To protect against this, during the period of recruitment to the study, interim analyses of major endpoints will be supplied, in strict confidence, to an independent Data Monitoring Committee (DMC) along with updates on results of other related studies, and any other analyses that the DMC may request.

The DMC will advise the chair of the TSC if, in their view, any of the randomised comparisons in the trial have provided both (a) “proof beyond reasonable doubt” that for all, or for some, types of participant one particular treatment is definitely indicated or definitely contraindicated in terms of a net difference in the major endpoints, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results. Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least $p<0.001$ (similar to Haybittle-Peto stopping boundary) in an interim analysis of a major endpoint may be needed to justify halting, or modifying, the study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed. The TSC can then decide whether to close or modify any part of the trial. Unless this happens, however, the TMG, TSC, the investigators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results.

A trial specific charter has been drawn up to define the remit and terms of reference of the TSC and DMC, which will be agreed by the Chief Investigator, the TSC and DMC members before the commencement of the study.

14.7 Project Management

Birmingham Women’s and Children’s NHS Foundation Trust (BWCNFT) will be the trial sponsor and host organisation. Honorary contracts are in place with the University of Birmingham who employ the Chief Investigator (SK). Subcontracts will be put into place between the BWCNFT and the University of Birmingham Clinical Trials Unit (BCTU – coordinating centre), detailing the budget resources allocated, the responsibilities and expected contributions of each party. Agreements with the clinical applicants will also be put into place.

Contracts will be agreed between BCTU and the University of Aberdeen for the telephone randomisation system. BWCNFT will contract with Sharp Clinical Services for the blinding, labelling, production and distribution of oxytocin.

Day to day management will be undertaken by BCTU with the Trial Manager and the Lead Midwife responsible for the sites. Regular meetings will take place to monitor progress with the CI and representatives from BCTU and the Sponsor as required. The full co-applicant group will meet regularly throughout the duration of the trial.

14.8 Archiving

Storage will be authorised by the Sponsor following submission of the end of trial report. Destruction of essential documents will require authorisation from the BWCNFT as Sponsor.

Principal Investigators are responsible for the secure archiving of essential trial documents for their site, according to the local policy at that site. All essential documents will be archived for a minimum of 25 years after completion of trial. Destruction of essential documents will require authorisation from BWCNFT as Sponsor.

Trial data will be stored under controlled conditions for at least 3 years after closure. This will allow adequate time for review and reappraisal, and in particular with the HOLDS trial, form the basis for further follow-up research. Any queries or concerns about the data, conduct or conclusions of the trial can also be resolved in this time. Long-term offsite data archiving facilities will be considered for storage after this time. BCTU has standard processes for both hard copy and computer database legacy archiving, including anonymisation of trial data.

15 Organisation and responsibilities

To ensure the smooth running of the trial and to minimise the overall procedural workload, it is proposed that each participating centre should designate individuals who would be chiefly responsible for local co-ordination of clinical and administrative aspects of the trial.

All investigators are responsible for ensuring that any research they undertake follows the agreed protocol, for helping care professionals to ensure that participants receive appropriate care while involved in research, for protecting the integrity and confidentiality of clinical and other records and data generated by the research, and for reporting any failures in these respects, adverse reactions and other events or suspected misconduct through the appropriate systems.

15.1 Centre eligibility

Centres will be eligible to recruit to the HOLDS trial if they are:

- Compliant with current NICE Guidance for the care of nulliparous women with delay in labour
- Use standard dose oxytocin regimen routinely
- A research active unit- with a track record of intrapartum research recruitment
- Able to nominate a research midwife, ideally from Delivery Suite (DS) staff, to lead on the HOLDs study at site
- Can provide Pharmacy and Neonatal leads
- Agree to recruit women to the iHOLDS trial

- A site's participation in the trial will only be continued if pre-specified and agreed numbers of women have been recruited.

15.2 Principal Investigator at each centre

Each Centre should nominate an obstetrician to act as the local Principal Investigator and bear responsibility for the conduct of research at their centre. Close collaboration between all clinical teams is particularly important in HOLDS, as women are cared for by midwives and obstetricians.

The local Principal Investigator is responsible for the overall conduct of the trial at the site and to ensure compliance with the protocol and any amendments. The PI must have up to date NIHR Good Clinical Practice (GCP) training and a copy of the training certificate should be provided to the HOLDS Trial Office. In accordance with the principles of International Committee on Harmonisation Good Clinical Practice Guidelines (ICH GCP) the following areas listed in this section are also the responsibility of each Investigator. Responsibilities may be delegated to an appropriate member of trial site staff. Delegated tasks must be documented on a Delegation Log (or Training Log) and signed by all those named on the list prior to undertaking applicable trial-related procedures. The listed responsibilities are:

- Actively promote and support the trial
- Ensure they are aware of the Data Protection Act, The Caldicott Principles and relevant Trust/Health Board information policies
- Anonymise participant data where possible and hold it in accordance with the Data Protection Act
- Consent must be sought before using the information for any other purpose
- Counter sign completed data collection forms
- Oversee completion and submission of daily temperature logs from Delivery Suite to the HOLDS Trial Office on at least a monthly basis
- Ensure they are aware of the Health and Safety act and Trust policy - including the implications for themselves and participants
- Notify the trial office of all reportable Serious Adverse Events (SAEs), within 24 hours of HOLDS local research team becoming aware (see *Section 11*)
- Supply any additional information required by the HOLDS Trial Office and supply any additional information to the MHRA and the Ethics Committee, via the Trial Office, as necessary and requested by the Chief Investigator (CI)
- Report any suspected misconduct to the HOLDS Trial Office
- Keep the original signed consent form in the Investigator Site File. Additional copies should be taken to give to the participant, file in the medical notes and return to the HOLDS Trial Office
- Ensure completion and appropriate storage of all study related data collection forms
- Ensure that only researchers with a contractual relationship with the Trust hosting the research make contact with participants. There are procedures in place for issuing honorary contracts
- Consider client diversity and be responsive to their information needs
- Disseminate research findings to relevant bodies
- Able to arrange for secure storage of the trial related documents for 25 years.

15.3 Research Midwife at each site

Each participating centre should also designate one midwife as local Midwife Coordinator, ideally based on Delivery Suite. The Research Midwife must have up to date NIHR Good Clinical Practice (GCP) training. We realise the importance of training staff so they can explain the study and answer any questions. Prescription of oxytocin as part of the induction process can occur at any time during the day or night and this means that all staff (especially Midwives) need to have knowledge of the trial which enables them to identify potentially eligible women and to feel comfortable introducing the study and answering any questions the woman and her birth partner(s) may have. Following confirmation of eligibility and the woman agreeing to take part, the Midwife needs to be familiar with the consent, randomisation, treatment allocation procedures and subsequent care required for the trial. Midwives are uniquely placed to be able to undertake these tasks as they are experienced in the management of women receiving oxytocin as part of the induction process as this is common place on Delivery Suites.

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- The HOLDS nominated Research Midwife at site will be responsible for:
- Training site staff on trial related procedures
- Actively promoting the trial and maintaining the profile within each unit
- Troubleshooting challenges
- Collecting outcome data and ensuring accurate capture of outcome data, to minimise the impact on busy clinical staff
- Maintaining oversight of IMP accountability and active temperature monitoring where maintained on Delivery Suite, including submission of data in a timely manner of daily temperature logs from Delivery Suite on at least a monthly basis, sending a copy of the paper log by email to the HOLDS Trial Office
- Receiving, acting upon and distributing information received via HOLDS updates and newsletters
- Representing the site at training and progress meetings approximately every six months.

15.4 Management of sites

The TMG will actively manage recruitment and respond to fluctuations quickly by contacting the units directly. The (approximately) 30 HOLDS midwives will be supported by an external Lead Midwife who, together with the Chief Investigator and Trial Manager, will undertake site visits to more fully understand recruitment issues. Midwives will attend training days to learn from sites that are recruiting well, and to support and rejuvenate them for their role. Recruitment processes and documentation were developed during the pilot study and are aligned with clinical practice and written in clear understandable language, thus increasing the chances of success. Incentives will be provided which will include mugs, pens, hand creams and light refreshments together with a monthly prize draw (£10) for Delivery Suites, with other incentives suggested by the midwives.

15.5 Site set up and initiation

Start-up visits at each participating centre will be undertaken, remotely or in person, by the lead HOLDS research midwife, the HOLDS trial manager or the Chief Investigator from the HOLDS Trial Team before recruitment of women is permitted. At this visit Pharmacy arrangements will be explored. Recruitment cannot begin within any site until all required permissions are in place, training has been given, and women have received the antenatal letter regarding the trial.

Additional training will be delivered to clinical staff (Clinical Midwives and Obstetricians) working on the study (see *Section 15.8 Training in the Maternity Units* for more details).

Regular site visits will be made by the Lead Research Midwife/CI/Sponsor representative/Trial Manager to ensure adherence to the protocol and to deal with any specific site issues. Regular study days will be undertaken to ensure that obstetricians and midwives involved with the study are fully apprised of issues such as informed consent, data collection, follow-up, and changing regulations.

15.6 The HOLDS Trials Office at BCTU

The HOLDS Trial Office at BCTU is responsible for providing all trial documentation, including the trial folders (Investigator Site File and Pharmacy File) containing printed documents and the update slides. These will be supplied to each collaborating centre after all relevant approvals have been obtained. Additional supplies of any printed material can be obtained on request. The Trial Office is responsible for collection and checking of data (including reports of serious adverse events), for reporting of serious and unexpected adverse events to the sponsor and/ or regulatory authorities and for analyses. The Trial Office will help resolve any local problems that may be encountered in trial participation.

15.7 Research Governance

The conduct of the trial will be according to the principles of the International Committee on Harmonisation, Good Clinical Practice Guidelines (ICH GCP).

All centres will be required to sign a Clinical Site Agreement, detailing their commitment to accrual, compliance, Good Clinical Practice, confidentiality and publication. Deviations from the agreement will be monitored and the TMG will decide whether any action needs to be taken, e.g. withdrawal of funding, suspension of centre.

Researchers not employed by an NHS organisation should hold an NHS honorary contract for that organisation.

15.8 Training in the Maternity Units

We understand the importance of training for staff and will undertake multidisciplinary training (including regular updates/reminders). Delay in labour can occur at any time during the 24 hour day and this means that all staff (especially midwives) need to have knowledge of the trial which enables them to identify potentially eligible women and to feel comfortable introducing the trial and answering any questions the woman and her carers may have. Following confirmation of eligibility and the woman agreeing to take part, the midwife needs to be familiar with the randomisation, treatment allocation procedures and subsequent care required for the trial. Midwives are uniquely placed to undertake these tasks as they are experienced in the management of women having oxytocin for delay in labour which is common place on Delivery Suites.

The trial will use a cascade model whereby the Trial team will devise appropriate training with input from NIHR GCP Facilitators, and deliver this training to the PI and Research midwives in each centre. These staff will then ensure that this training is cascaded within units to all relevant clinical staff. This training will be updated and reviewed on a regular basis with regular refresher sessions for all involved. Training for clinical staff may alternatively be delivered via an online training platform setup by the BCTU. Attendance is documented on an electronic Training Log and signed off by the PI to confirm delegation of duties.

16 Regulatory and Ethical Approval

16.1 Ethical and Trust Management Approval

The Trial has a favourable ethical opinion from West Midlands - Edgbaston Research Ethics Committee (REC), (16/WM/0014) confirming that the trial design respects the rights, safety and wellbeing of the participants.

The Trial Office will support sites by completing where appropriate and providing information through the HRA or site specific information process (depending on which system is in place at their trust) The local Principal Investigator will be responsible for liaison with the Trust management with respect to locality issues and obtaining the necessary signatures at their Trust.

As soon as Trust approval has been obtained, the Trial Office will send a folder containing all trial materials to the local Principal Investigator and site research team. Potential trial participants can then start to be approached once the HOLDS Trial Office issues formal site activation. Site Initiation visits will be undertaken before recruitment begins.

Within 90 days after the end of the trial, the Chief Investigator, on behalf of the Sponsor, will ensure that the REC and MHRA is notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The Chief Investigator will supply the Sponsor with a summary report of the clinical trial, which will then be submitted to the REC and MHRA within one year after the end of the trial.

16.2 Funding and Cost implications

The research costs of the trial are funded by a grant from the NIHR Health Technology Assessment Programme awarded to the BWCNFT.

The trial has been designed to minimise extra 'service support' costs for participating hospitals, with no extra visits to hospital and no extra tests. Additional costs, service support costs and excess treatment costs associated with the trial, e.g. gaining consent, are estimated in the SoeCAT. These costs should be met by accessing the Trust's Support for Science budget via the Local Comprehensive Research Network (CRN).

16.3 Indemnity

This is a clinician-initiated trial. The Sponsor (BWCNFT) holds the relevant insurance for Clinical Trials (negligent harm). Participants may be able to claim compensation, if they can prove that the BWCNFT has been negligent. However, as this clinical trial is being carried out in a hospital setting, NHS Trusts, NHS health Boards and Non-Trust Hospitals have a duty of care to the participants being treated. Compensation is only available *via* NHS indemnity in the event of clinical negligence being proven.

Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the CI, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office. There are no specific arrangements for compensation made in respect of any SAE occurring though participation in the trial, whether from the side effects listed, or others yet unforeseen.

Hospitals selected to participate in this trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary should be provided to BWCNFT, upon request.

17 Public and Patient Involvement

17.1 The aims of active involvement in this project

Ultimately the aim of PPI engagement is to undertake research 'with women' and not 'on women' [NCT/AIMS 1997], to develop a trial that is acceptable to women in labour and that we assess whether high dose regimens of oxytocin for confirmed delay in the first stage of labour do reduce CS. This research topic was originally prioritised by the NICE Intrapartum Care Guideline in 2007, which included a strong PPI element. One of the service users on the Guideline Development Group became a co-applicant on our pilot study (PB.PG.0407.13193). Her involvement has been integral to the research design, consent and recruitment processes and information for women developed during the pilot and proposed for this trial. This individual has stepped down due to family commitments and is replaced by Ruth Hewston. She is an equal member of the co-applicant group. We also have PPI representation on the TSC.

Parents and Researchers Involvement in Maternity and Early pregnancy (PRIME) group is a PPI group set up in collaboration with the University of Birmingham Collaboration for Leadership and Applied Health Research and Care (CLAHRC) and has a geographical and socio-economically diverse spectrum of women with experience of Maternity Services use and their partners. The PRIME group reviewed the trial documentation prior to the start of the trial.

The HOLDS website with hyperlinks to NCT home page will make full use of social networking platforms (i.e. Twitter to provide study updates). We will publish project progress and results through press releases from our University, Sponsor, HTA website and the project website.

17.2 A description of the methods of involvement

From its conception this trial has had women at its heart. Providing best evidence of the dose of oxytocin to reduce CS for women delayed in labour is important as the known short and longer term effects of CS are well described. The importance we attach to the perspective of the user is clearly demonstrated by the qualitative methods we used during the pilot to explore women's understanding of the trial and the consent processes which suggested that these processes we will use are acceptable to women. We will involve PPI in approach for trial participation, in review of trial documentation and in staff training.

A summary of the results will be posted on the website as soon as they are available and we will ensure use of the social networking platforms described above. Participants will also be informed that they can access the results through their local library.

18 Reporting, publications and notification of results

18.1 Authorship and publication policy

As Sponsor, all data arising from this trial is owned by BWCNFT. The results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the CI and authorship will be determined by the trial publication policy. The trial results will be published in the NIHR Health Technology Assessment journal. A link to this manuscript, and any other publications prepared by the CI in relation to the HOLDS trial, will be made available on the trial website.

Any secondary publications and presentations prepared by Investigators must be reviewed and approved by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of the University of Birmingham. Intellectual property rights will be addressed in the Clinical Study Site Agreement between Sponsor and site.

18.2 Ancillary studies

It is requested that any proposals for formal additional studies of the effects of the trial treatments on some participants (e.g. special investigations in selected hospitals) be referred to the Trial Management Group for consideration. In general, it would be preferable for the trial to be kept as simple as possible, and add-on studies will need to be fully justified.

19 History of Amendments

24th February 2016

Response to review by the Ethics Committee

- More detail was added in the PILs regarding the side effects of Syntocinon related to tachysystole and hyperstimulation, and that results could be accessed through local libraries, as well as the website
- We clarified the way in which sites will unblind participants in the unlikely event that is required
- We clarified two data items – deleted the collection of Apgar score at 1 minute, as we will not use the data, and will collect Apgar score at 5 minutes
- We clarified that we will collect information on the numbers of women who are catheterised due to urinary retention
- We added 'Student Midwife or Maternity Support Worker' who have been HOLDS trained to those who could ring the automated telephone service to randomise women
- We added the actual email and website where they appeared in the PILs and Protocol
- We made some amendments to the Lay Summary as a result of recent feedback so it the same as on the HTA website

Substantial Amendment 1: 16th August 2016

- Made in response to review by the MHRA
    - Changes to the description of the monitoring in labour that is undertaken to both mother and baby
    - Clarity of the descriptions for adverse drug reactions and events and reporting arrangements
- Addition of a minimisation algorithm to the randomisation
- Addition of exclusion criteria of full cervical dilation of the woman
- Faxing of consent and randomisation forms to the Trial Office for in house monitoring purposes
- Clarity around the data collection items (for mother: use of epidural analgesia during labour, degree of perineal trauma (First, second, third, fourth), active management of third stage of labour, for the baby: gender and birthweight, resuscitation, reason for review on the postnatal ward (excluding routine baby check), reason and level of neonatal care, duration of respiratory support, days to full oral feeds, SARNAT grade)
- Membership of the Trial Steering and Data Monitoring Committees as these have been agreed by the NIHR
- Minor amendments and correction of minor mistakes found within the protocol

Non Substantial Amendment 2 - changes to wording on HOLDS IMP dispensing label

Substantial Amendment 3

- Signature statement updated
- Confirmed randomisation phone number
- Management group membership updated
- New TSC members have been agreed by the NIHR
- Definition of nulliparous added
- Further detail regarding the distribution of antenatal letters
- Clarification of making up solution with the study drug

- Clarification regarding communication to sites of co-enrolment and sponsor to sponsor agreements
- Further clarity regarding personnel and training requirement
- Update of details regarding the prescription of the IMP.
- Details regarding accountability and broken IMP vials
- Unblinding and withdrawal procedures clarified
- Update to safety section including removal of SPC which has been replaced by the RSI and clarification of safety reporting and responsibilities
- CRF`s as source data, method of data collection and time frames for completion of CRF`s and data transfer.
- Clarification of transfer of confidential data and confidential data collected
- Update of PI responsibilities
- Minor amendments and correction of minor mistakes found within the protocol
- Fetal monitoring terminology updated in line with updated NICE guidance

Non Substantial Amendment 4 – correction to typo error on the consent form

Non Substantial Amendment 5 – Establish a twitter account for clinicians

Non Substantial Amendment 6 – Addition of new sites and change of Principal Investigator

Substantial Amendment 7 – Halt of the trial

Non Substantial Amendment 8 – Addition of site

Substantial Amendment 9

- Sponsor organisation - address updated
- Update of TSC , DMC and co-applicant and research fellow details
- Inclusion criteria updated
- Clarification surrounding dilatation of 8-9cm
- Clarification of IMP guidelines and temperature deviations
- Further detail regarding withdrawal and monitoring
- Update on SAE reporting, including the removal of reference safety information appendices
- Further detail regarding breach reporting
- Minor amendments and correction of minor mistakes found within the protocol

Substantial Amendment 10

- Sponsor organisation - address updated
- Update of TSC , DMC and co-applicant and research fellow details
- Inclusion criteria updated
- Clarification surrounding dilatation of 8-9cm
- Clarification of IMP guidelines and temperature deviations
- Further detail regarding withdrawal and monitoring
- Update on SAE reporting, including the removal of reference safety information appendices and reference to HOLDS reference safety information
- Further detail regarding breach reporting
- Minor amendments and correction of minor mistakes found within the protocol

Non Substantial Amendment 11 - Change of PI at Site

Substantial Amendment 12

- Halt of the Trial
- Updated version of reference safety information and SPC reference
- Amendment additions updated
- General typographical errors corrected

Non-Substantial Amendment 13 (NSA-13) dated 27th April 2021

- Addition of new sites
- Change of PI at existing approved sites
- Removal of existing approved sites

Substantial Amendment 14 (SA-14) dated 27th April 2021

Protocol version: 8.0 dated 15th April 2021

Section	*Summary of key changes*
N/A	• Trial logo replaced • Minor amendments and correction of minor mistakes found within the protocol
3 Contacts and Roles	Contacts updated, including the removal of contact details for committee members
5 Background	Updated with data from a published trial
6 Trial Aim and Objectives	Updated to include summary of pilot study
7 Trial Design	Changes to eligibility criteria
8 Treatment Allocation	• Instructions added for daily IMP temperature logging and reporting • Addition of the following sections: Drug interaction or contraindications, treatment modification, cessation of treatment/continuation after the trial • Withdrawal of trial/treatment and change of status within the trial section replaced
10 Adverse Event Reporting	Restructuring of section and addition of new information and instructions for SAE reporting
11 Data Management	• Addition of case report form schedule and summary of data collection points, personnel and training requirements • Removal of duplicated section (long term storage of data)
12 Statistical Methods and analysis	• Additions to description of statistical analysis outline plan • Amendments to primary outcome analysis and subgroup analysis sections
13 Data Access and Quality Assurance	Addition of ethical considerations section
14 Organisation and Responsibilities	Update to centre eligibility rules, PI and Research Midwife responsibilities
15 Regulatory and Ethical Approval	Amendments to funding and cost implications section regarding financial support for sites
17 Reporting, Publications and Notification of results	Replaced text for authorship and publication policy

Non-Substantial Amendment 15 (NSA-15) dated 7th June 2021

Protocol version: 8.0a dated 27th May 2021

- Addition of inclusion criteria "with ruptured membranes".

Non-Substantial Amendment 16 (NSA-16) dated 12th October 2021

Protocol version: 8.0b dated 8th October 2021

Protocol Section	*Summary of key changes*
N/A	Minor amendments and correction of minor mistakes found within the protocol
Trial Schema	Updated and moved to earlier section of protocol
4 Contacts and Roles	• Trial management contact details updated • DMC Statistician replaced
9 Trial Treatment/ Intervention	• Treatment regimen tables merged to include infusion rate for 50 ml and 500 ml dilution • Instruction added to remove 2 ml of diluent prior to adding oxytocin if required • Details regarding temperature monitoring clarified • Summary of HOLDS data collection section removed (duplicated in section 12 Data Management)
12 Data Management	Personnel and training requirements table updated
15.8 Training in the Maternity Units	Details regarding online training platform added

Non-Substantial Amendment 17 (NSA-17)

- Update to Organisation Information Document

Non-Substantial Amendment 18 (NSA-18)

- Addition of new site (Royal Victoria Infirmary, Newcastle)
- Change of PI at Great Western Hospital, North Tees and Birmingham Women's Hospital

Non-Substantial Amendment 19 (NSA-19)

- Updates to PIL and ICF
- Addition of 7 trial promotional posters

Substantial Amendment 20 (SA-20) dated 10th October 2022

- Protocol version: 9.0 dated 10th October 2022

Protocol Section	*Summary of key changes*
N/A	Minor amendments and correction of minor mistakes found within the protocol
1 Trial Summary	Target population amended to remove definition of confirmed delay
Trial Schema	Updated to include recruitment or women where delay in labour is suspected
4 Contacts and Roles	• Link to trial database added • TMG and TSC contacts updated
6 Background	Further details added to timepoint of commencing treatment
8 Trial Design	Amended to include recruitment of women with suspected delay
9 Trial Treatment/ Intervention	Further details added for reporting minor temperature deviations and missing temperature readings
11 Adverse Event Reporting	• Hyponatraemia added as a maternal outcome • Definition for serious maternal hyponatraemia added
12 Data Management	CRF schedule updated to return ICF copies by post or secure email

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