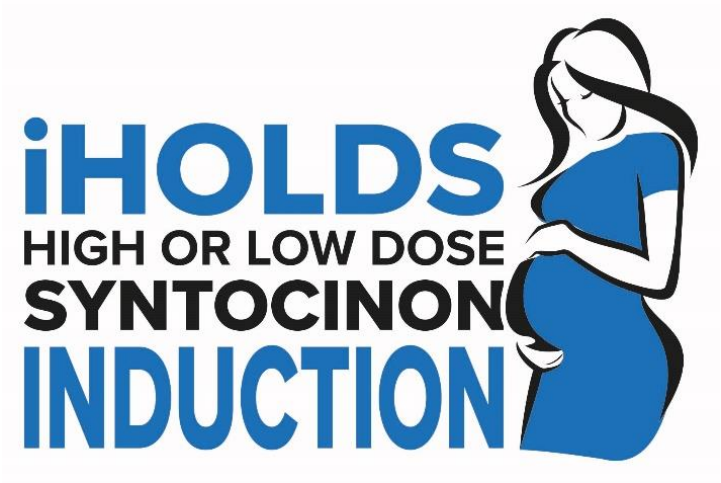
UNIVERSITY OF BIRMINGHAM | BCTU Birmingham Clinical Trials Unit

TRIAL PROTOCOL



High or Low Dose Syntocinon for induction of labour in nulliparous women: a double blind, randomised controlled trial

Version Number:	1.0b
Version Date:	7th October 2021

This protocol has regard for the HRA guidance and is compliant with SPIRIT

FUNDED BY NIHR | National Institute for Health Research

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

IRAS ID:278209 EudraCT number: 2020-004387-26 ISRCTN number: 79220656

Protocol Development

Protocol Amendments				
The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version:				
Amendment number	**Date of amendment**	**Protocol version number**	**Type of amendment**	**Summary of amendment**
NSA-01	04/06/2021	1.0a	Non-substantial	See protocol Section 25
NSA-02	12/10/2021	1.0b	Non-substantial	See protocol Section 25

Funding and Support in Kind	
Funder (s) (Names and contact details of all organisations providing funding and/or support in kind for this trial)	**Financial and non-financial support given:**
National Institute for Health Research (NIHR)	Financial
Funding Scheme (if applicable)	Health Technology Assessment Programme
Funder's reference number	17/137/02
Department of Health and Social Care disclaimer: The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care	

Protocol Sign Off

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 iHOLDS Trial
Protocol Version Number:	1.0b
Protocol Version Date:	7th October 2021
Chief Investigator Name:	Sara Kenyon
Signature and date:	 07 / Oct / 2021
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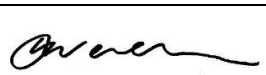
Signature and date:	 07 / Oct / 2021

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

Reference Numbers	
EudraCT number	2020-004387-26
Sponsor number	19/BW/MAT/PO/277
ISRCTN reference number	79220656
IRAS reference number	278209

PI Signature Page

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

I agree to ensure that the confidential 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.

This protocol has been approved by:

Trial Name:	The iHOLDS Trial
Protocol Version Number:	1.0b
Protocol Version Date:	7th October 2021
Site Name:	
Principal Investigator Name:	
Signature and Date:	_____ __ __/__ __/__ __ __ __

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Trial website	www.birmingham.ac.uk/iHOLDS
Trial social media	Twitter: @iHOLDSTrial

ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
APR	Annual Progress Report
AR	Adverse Reaction
ARM	Artificial rupture of membranes
BCTU*	Birmingham Clinical Trials Unit
BSS-RI	Birth Satisfaction Scale-Revised Indicator
BWCNFT* or BWH	Birmingham Women's and Children's NHS Foundation Trust
CHaRT	Centre for Healthcare Randomised Trials
CI*	Chief Investigator
CRF	Case Report Form
CRN	Comprehensive Research Network
CS	Caesarean Section
CSR	Caesarean Section Rate
CTIMP	Clinical Trial of an Investigational Medicinal Product
DCF	Data Clarification Form
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
FBS	Fetal blood sampling
GCP	Good Clinical Practice
GDMC	Gestational Diabetes Mellitus
GDPR	General Data Protection Regulation
HDU	High Dependency Unit
HRA	Health Research Authority
HTA	Health Technology Assessment
ICF	Informed Consent Form
ICH GCP	International Committee on Harmonisation Good Clinical Practice Guidelines
ISF	Investigator Site File

Abbreviation	Term
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
PH	Proportional Hazard
PI*	Principal Investigator
PIL	Participant Information Leaflet
PPI	Patient and Public Involvement
PPIE	Patient and Public Involvement and Engagement
PSS	Prescribed Specialised Services (Tool)
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SoECAT	Schedule of Events Cost Attribution Template
SPC	Summary of Product Characteristics
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SROM	Spontaneous rupture of membranes
STAN	ST analysis
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVM	Spontaneous vaginal birth
TMF	Trial Master File
TMG	Trial Management Group

Abbreviation	Term
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UoB	University of Birmingham
WHO	World Health Organisation

*See *Definitions* table below for description

DEFINITIONS

Term	Abbreviation	Description
Apgar Score	N/A	A measure of the physical condition of a newborn infant.
Birmingham Clinical Trials Unit	BCTU	The coordinating centre for the trial.
Birmingham Women's and Children's NHS Foundation Trust	BWCNFT	The Sponsor for the trial.
Chief Investigator	CI	A suitably medically qualified person designated overall responsibility for the design, conduct and reporting of the trial.
High or Low Dose Syntocinon for Delay in labour	HOLDS Trial	Trial to be run within participating iHOLDS sites for nulliparous women with delay in labour. EudraCT number: 2015-005537-50.
Principal Investigator	PI	A suitably medically qualified person who appears on the delegation log at site and takes responsibility for the conduct of the trial in the Trust/Health Board.
Sarnat Grading scale	SARNAT	A classification scale for hypoxic-ischaemic encephalopathy of a newborn infant.
Source data	N/A	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

TRIAL SUMMARY

Title: High or low dose Syntocinon, for induction of labour in nulliparous women: a double blind, randomised controlled trial (The iHOLDS Trial)

Objectives: To provide robust evidence of clinical effectiveness and costs of high dose compared to standard dose regimen of Syntocinon (oxytocin) for nulliparous women when prescribed during induction of labour

Trial Design: A randomised, double blind, multi-centre study, with a health economic evaluation and an internal pilot

Setting: Delivery suites at secondary and tertiary level hospitals across the UK

Participant Population and Sample Size: Nulliparous women who are undergoing induction. The sample size will be 2400 women, allowing 90% power (p=0.05) to detect an absolute risk reduction of 6% (equivalent to a 20% relative reduction), assuming the average caesarean section rate (CSR) in the standard-regimen group to be approximately 30%. This includes a conservative 4% inflation for any loss to follow-up or withdrawals

Eligibility Criteria Summary:

Inclusion Criteria: All nulliparous women with a singleton pregnancy undergoing induction of labour for whom oxytocin is prescribed as part of the induction process

Exclusion Criteria: Nulliparous women who have existing cardiac disease, bleeding disorders, who have had previous uterine surgery, or significant antepartum haemorrhage. Those under 16 years of age or with a known contra-indication to oxytocin therapy

Interventions: High dose regimen of oxytocin (4mU/min increasing every 30 minutes to a maximum of 64mU/min) compared with a standard dose regimen (2mU/min increasing every 30 minutes to a maximum 32mU/min)

Outcomes:

Primary Outcome: Caesarean Section Rate (CSR)

Secondary Outcomes: Maternal and neonatal birth outcome data that are routinely collected and include the recently published Core Outcome set, and a quantitative assessment of maternal psychological outcomes using validated tools two weeks after birth

Cost Comparison Outcomes: The aim of the cost comparison will be to assess the costs associated with a high dose regimen of oxytocin compared with the current standard dose, (on the basis of a within-trial study). An NHS/Prescribed Specialised Services (PSS) tool perspective will be adopted in line with NICE recommendations. Resource use and costs will be collected prospectively in both arms of the trial. Information on unit costs or prices will then be required to attach to each resource item in order that an overall cost per woman can be calculated.

Trial Schema

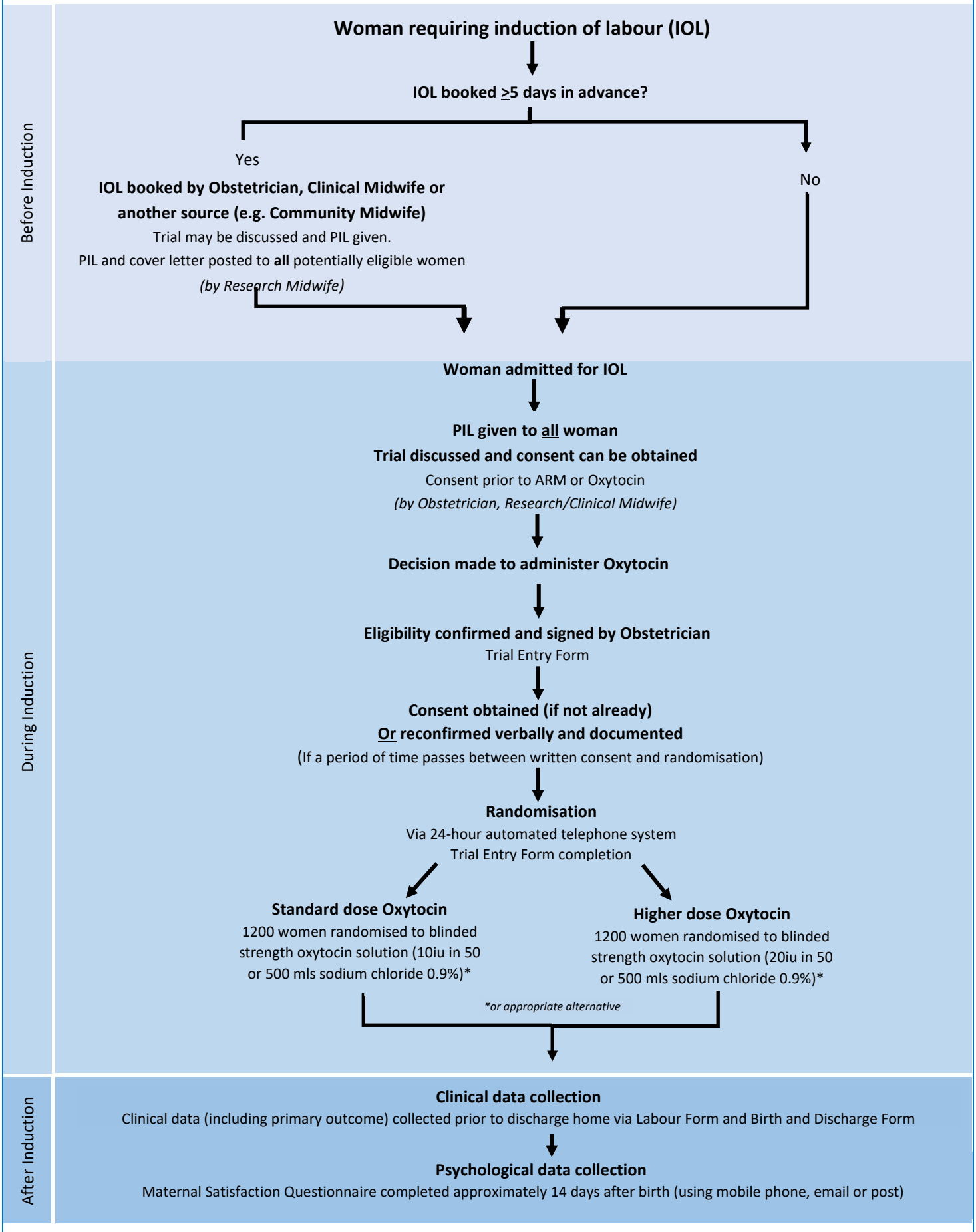

TABLE OF CONTENTS

List of Tables

1. BACKGROUND AND RATIONALE

1.1 Background

Evidence regarding the optimal dose of oxytocin in women who require it for induction of labour is very limited, with mixed results and unclear findings for clinically relevant indicators to help guide practice. Synthetic oxytocin is a man-made chemical that is identical to a natural hormone called oxytocin, and is used during induction to stimulate uterine contractions.

The most recently available UK guidance on synthetic oxytocin use for induction of labour is the 2001 guidelines from the Royal College of Obstetricians and Gynaecologists[1]. The recommendations are noted to be based on low quality evidence:

- Oxytocin should not be started for six hours following administration of vaginal prostaglandins.
- Amniotomy should be performed where feasible prior to commencement of an infusion of oxytocin.
- When induction of labour is undertaken with oxytocin the recommended regimen is:
  - A starting dose of 1–2 milliunits (mU) per minute
  - Increased at intervals of 30 minutes or more.
- The minimum dose possible of oxytocin should be used and this should be titrated against uterine contractions aiming for a maximum of three to four contractions every ten minutes.
- In the Summary of Product Characteristics (SPC) the licensed maximum dose is 20 milliunits per minute.
- If higher doses are used the maximum dose used should not exceed 32 milliunits per minute.

An Evidence Synthesis into which method is best for the induction of labour undertaken by Alfirevic[2] in 2016 included a systematic review, network meta-analysis and cost-effectiveness analysis. In brief, this analysis found that intravenous oxytocin combined with amniotomy had the best chance of all methods of achieving vaginal delivery within 24 hours of induction. However, the review did not separate out these findings in terms of the dose of oxytocin.

Budden[3] led the Cochrane review into high versus low dose oxytocin infusion regimens for induction of labour at term. This searched for publications up to August 2014 and included 9 trials (n=2,391 women). High dose oxytocin regimen was defined as at least 100 mU oxytocin in the first 40 minutes, with increments delivering at least 600 mU in the first two hours. A low dose oxytocin regimen was less than 100 mU oxytocin in the first 40 minutes, and increments delivering less than 600 mU total in the first two hours. Results demonstrated no significant differences in rates of vaginal delivery not achieved within 24 hours, caesarean section, serious maternal morbidity or death, serious neonatal morbidity or perinatal death or any other secondary outcomes. No trials reported the number of women with uterine hyperstimulation with associated fetal heart rate changes but there was a significant increase in hyperstimulation in the high dose group. Removal of high bias studies found a significant reduction in time to delivery.

Three further primary studies[4,5,6] are of varying quality with mixed results. There are no ongoing trials investigating differing doses used as part of the induction process registered on the WHO International Clinical Trials Registry or Clinical Trials.gov.

This trial to determine whether a higher starting dose of oxytocin reduces the risk of caesarean section without increasing adverse maternal or neonatal outcomes has been commissioned by the Health Technology Assessment (HTA) Programme of the UK NIHR.

1.2 Trial Rationale

1.2.1 Justification for Participant Population

The participant population is nulliparous women undergoing induction of labour for whom oxytocin is prescribed as part of the induction of labour process and whom clinical staff are willing to randomise.

The numbers of women undergoing induction of labour at term is steadily increasing with current estimates suggesting that at least 70,730 (34%) of first time mothers undergo induction of labour in the UK each year[7].

This is undertaken for a variety of reasons, the most common being post maturity[8] and following pre-labour rupture of the membranes at term[9]. However recent evidence has further increased the rate of induction, for example women with hypertension[10], diabetes in pregnancy[11], or advanced maternal age[12].

The preferred method of induction of labour is initially to use vaginal prostaglandins or other methods to ripen the cervix. While some women will go into labour with prostaglandin alone, the majority of nulliparous women require artificial rupture of the membranes, followed by oxytocin to stimulate contractions. The national guidance on induction of labour is currently being updated, however a recent evidence synthesis did not review the dose regimen of oxytocin[2].

Data on the number of women having oxytocin as part of the induction process are unavailable nationally but we have undertaken an audit of 22 Maternity Units already collaborating on another trial (the HOLDS trial – EudraCT number: 2015-005537-50) which suggests 60% of first time mothers require oxytocin during the induction process (approximately 42,438 births nationally). These women have a relatively high risk of unplanned caesarean section (CS) (approximately 30%) and making sure this 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 an increased risk of CS in subsequent pregnancies and therefore increased cost to the NHS[13,14,15].

The increasing numbers of women undergoing induction of labour presents an escalating logistical problem for maternity services. Induction is more resource intensive than spontaneous labour because the process is longer and women need more intensive monitoring. While there is evidence that induction of labour compared to spontaneous labour may reduce the risk of CS overall, this is less clear for nulliparous women[16] and there is evidence suggesting induction of labour at term is associated with increased risks of emergency CS[17].

For physiological and safety reasons, we have chosen to include only nulliparous women in this trial. Oxytocin is used to stimulate uterine contractions in two clinical scenarios; to initiate and maintain contractions during induction, and to improve contractions that are ineffective in spontaneous labour which is delayed. Multiparous women who have undergone labour before, particularly if they have achieved a vaginal birth, are more sensitive to oxytocin and it therefore needs to be used with greater caution than in nulliparous women as its use is more likely to lead to tachysystole and hyperstimulation, fetal compromise and, rarely, uterine rupture. For these reasons, the use of oxytocin may in fact lead to an increased risk of caesarean section because of fetal compromise and so multiparous women are excluded.

1.2.2 Justification for Design

This is a multicentre, randomised, double blind, controlled trial, with cost comparison and internal pilot to ensure ability to recruit to the study.

The multicentre design is to increase generalisability and also to recruit more efficiently. The randomisation and double blind design will ensure baseline characteristics are similar and that any differences between the group's outcomes can be attributed to the intervention. Blinding clinical staff is particularly important as knowing whether the woman has been allocated to standard or high dose oxytocin regimen is likely to influence clinical care.

1.2.3 Choice of Intervention

Use of oxytocin as part of the induction of labour process is an everyday occurrence on UK Delivery Suites and it has been used since the 1960s. This is a situation clinical staff are used to managing. Oxytocin is licensed for this specific indication and is given by intravenous (IV) infusion, which is discontinued after the birth of the baby. 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 establishment of effective uterine contractions, dilation of the cervix and vaginal birth. When oxytocin is being given, women will be more intensively monitored and have one to one care from a Midwife.

There is currently national guidance[1] regarding the standard dose regimen of oxytocin for women who are prescribed it as part of the induction process which defines the standard dose regimen (2 mU/min increasing every 30 minutes to a maximum 32m U/min). We will compare that to a high dose regimen (4 mU/min increasing every 30 minutes to a maximum of 64 mU/min). The high dose regimen has a higher starting dose, earlier

attainment of conventional maximum doses (at 2 hours rather than 4 hours) with the aim of the higher dose regimen being to achieve regular contractions more rapidly, rather than simply giving a higher total dose of oxytocin.

2. AIMS AND OBJECTIVES

2.1 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[18] 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 HTA. The pilot phase is planned to last 8 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 consider changes to processes)	Green (go ahead)	Actual target (Recruitment projection)
Recruitment				
Centres open	<13 <67% of actual	13-17 67-85% of actual	>17 85% of actual	20
Recruitment per centre per month (excluding two month lag phase in each centre)	<4.6 <67% of actual	4.6-5.8 67-85% of actual	5.8 85% of actual	6.8
Treatment adherence				
Proportion receiving allocated treatment	<80%	80-89%	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%	80-89%	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.

2.2 Main Trial Objectives

2.2.1 Aim

To determine the clinical effectiveness and costs of a high dose compared to the current standard dose regimen of oxytocin for nulliparous women for whom it is prescribed as part of induction of labour.

2.2.2 Primary Objective

To test the hypothesis that in nulliparous women who require oxytocin as part of induction of labour, a high dose regimen reduces the rate of caesarean section (CSR) by at least 20% compared with a standard dose regimen.

2.2.3 Secondary Objectives

- To assess additional important clinical maternal and neonatal outcomes.
- To compare the costs associated with the higher dose regimen of oxytocin, with those of the standard dose.
- To provide quantitative measurement of women's experiences of labour, birth and the early postnatal period two weeks after birth using a questionnaire to explore satisfaction with care and the experience of labour and birth using a validated tool (the Birth Satisfaction Scale- Revised Indicator (BSS-RI))[19].

2.2.4 Economic Aims and Objectives

The aim of the cost comparison will be to assess the costs associated with a high dose regimen of oxytocin compared with the current standard dose, (on the basis of a within-trial study). An NHS/PSS perspective will be adopted in line with NICE recommendations. Resource use and costs will be collected prospectively in both arms of the trial. Information on unit costs or prices will then be required to attach to each resource item in order that an overall cost per woman can be calculated.

2.2.4.1 Collection of Cost Data

NHS resource use and costs for women and infants will be collected prospectively in both arms via trial reporting mechanisms. This will include the costs associated with: i) giving the allocated dose of oxytocin by intravenous infusion; ii) maternal and fetal monitoring and titration of the dose; iii) delivery; iv) length and type of hospital inpatient stay (any adverse events will affect the length and type of hospital stay); v) any other NHS resource use for the woman and infant. Unit costs will be obtained and attached to resource items in order that a cost can be calculated for each patient. Unit costs will be obtained from published sources and centres participating in the trial. Published sources will include Unit Costs of Health and Social Care[20] and NHS Reference Costs[21]. Costs used in other relevant published sources will be sought for use in the sensitivity analyses.

2.2.5 Maternal and Psychological Health Objectives

Measurement of maternal psychological health. A questionnaire containing a validated tool to explore satisfaction with care and the experience of labour and birth (the Birth Satisfaction Scale- Revised Indicator (BSS-RI))[19].

3. TRIAL DESIGN AND SETTING

3.1 Trial Design

Multicentre, randomised, double blind, controlled trial, with cost comparison and eight month internal pilot to ensure ability to recruit to the study.

3.2 Trial Setting

Delivery suite in approximately 30 maternity units in the UK.

3.3 Identification of Participants

Nulliparous women who require oxytocin as part of the induction process will be eligible for recruitment and will be identified by clinical staff. Our pragmatic approach would be to include all eligible women whom clinical staff are willing to randomise and who consent to participation.

Recruiting women into trials of intrapartum care is challenging and we plan to follow national recommendations[22] regarding obtaining informed consent to participate in perinatal research where consent is time critical, and we will ensure that women have information about the study at the earliest opportunity.

A discussion between the woman and the clinical team will ideally take place whenever the induction is booked, and information, including a **Participant Information Leaflet (PIL)**, will be given/sent to women. For some women induction is booked in advance and for others the decision is made immediately prior to the process starting.

- If induction is booked in advance and time permits (5 or more days), the Research Midwifery Team will send information about the trial to the woman before her admission.
- When the woman is already undergoing induction, information will be given (including the PIL) and a discussion take place during the period of time that cervical ripening is undertaken. For most women this takes place (either as an inpatient or outpatient) for 24 hours or more.

When the induction process is underway, if the women agrees to participate in the trial she may be asked to provide written consent. Once the decision has been made to administer oxytocin and eligibility has been confirmed by an Obstetrician, consent will be obtained if not already, and the woman will be subsequently randomised to either high or standard dose regimen. Consent may be reconfirmed verbally if a period of time passes between written consent and randomisation which should be documented in the medical notes.

3.4 Assessment of Risk

All clinical trials can be considered to involve an element of risk and, in accordance with Birmingham Clinical Trials Unit (BCTU) operating procedures this trial has been risk assessed, to clarify any risks relating uniquely to this trial. A risk assessment has also been carried out by the Sponsor. These risk assessments conclude that the risk of participating in this trial is no higher than the risk of standard medical care and is therefore a Type A trial in accordance with risk-adapted approach to Clinical Trials of Investigational Medicinal Products (CTIMPs).

4. ELIGIBILITY

4.1 Inclusion Criteria

- Nulliparous women i.e. no previous births 24+0/40:
  - Who have a singleton cephalic pregnancy
  - With ruptured membranes undergoing induction of labour*
  - For whom prescribed oxytocin is indicated as part of the induction process
  - Whom clinical staff are willing to randomise
  - Who give written informed consent to participate prior to randomisation
  - Aged 16 years or above

*Induction of labour is defined as the process by which labour is started prior to its spontaneous onset by progressive cervical effacement and dilatation and/or artificial stimulation of uterine contractions, leading to active labour and birth. Women can be recruited at any gestation.

- Women can be recruited if labour is induced for any of the following reasons:
  - Post term induction
  - Spontaneous rupture of membranes (SROM)
  - Obstetric cholestasis
  - Pre- eclampsia/ hypertension
  - Diabetes / gestational diabetes (GDM)
  - Reduced fetal movements
  - Fetal growth disorder – either excessive or suboptimal growth
  - Advanced maternal age
  - Maternal request for induction
  - Other (at the Investigator's discretion)

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

4.2 Exclusion Criteria

- Nulliparous women who:
  - Are in the second stage of labour
  - Have any of the following conditions:
    - Existing cardiac disease
    - Bleeding disorders
    - Previous uterine surgery
    - Significant antepartum haemorrhage
  - Have a known contra-indication to oxytocin therapy as listed in the Summary of Product Characteristics (SPC) and in *section 7.2.1*.
  - Have received propess less than 30 minutes ago
  - Have received prostin less than 6 hours ago
  - Have a BMI of >40 at booking
  - Are participating in other interventional trials of an Investigational Medicinal Product (IMP) or procedure for induction of labour.

4.3 Co-Enrolment

Women may be recruited to non-interventional trials such as observational or qualitative studies for induction of 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. The Trial Office should be contacted in the first instance should this situation occur.

4.4 Centre Eligibility and Roles

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 coordination 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.

4.4.1 Centre Eligibility

Centres will be eligible to recruit to the iHOLDS Trial if they:

- Use standard dose oxytocin regimen routinely for induction of labour
- Are a research active unit with a track record of intrapartum research recruitment
- Able to nominate a Research Midwife from Delivery Suite staff to lead on the iHOLDS study at site
- Can provide Pharmacy and Neonatal leads
- Are able to participate in the HOLDS trial (EudraCT number: 2015-005537-50).

4.4.2 Principal Investigator at each Site

Each Site 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 iHOLDS, 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 iHOLDS 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 **Site Signature and Delegation 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
- Ensure they are aware of the Health and Safety Act and Trust/Health Board policy – including the implications for themselves and participants
- Notify the iHOLDS Trial Office of all reportable Serious Adverse Events (SAEs), within 24 hours of iHOLDS local research team becoming aware (see *Section 11 ADVERSE EVENT REPORTING)*
- Supply any additional information required by the iHOLDS Trial Office, or MHRA and the Ethics Committee via the Trial Office, as necessary and as requested by the Chief Investigator (CI)
- Report any suspected misconduct to the iHOLDS Trial Office
- Keep the original signed Informed Consent Form (ICF) in the Investigator Site File. Additional copies should be taken to give to the participant , file in the medical notes and return to the iHOLDS Trial Office
- Ensure completion and appropriate storage of all study related data collection forms

- Ensure that only researchers with a contractual relationship with the NHS Organisation hosting the research make contact with participants
- Ensure submission of data in a timely manner of daily temperature logs from Delivery Suite and Pharmacy on at least a monthly basis
- Consider client diversity and be responsible to their information needs
- Disseminate research findings to relevant bodies
- Able to arrange for secure storage of the trial related documents for 25 years
- Oversee completion and submission of daily temperature logs to the iHOLDS Trial Office.

4.4.3 Research Midwife at each Site

Each participating centre should also designate one Midwife as the local Midwife Coordinator, ideally based on the 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 Clinical 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.

The 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 and ensuring accurate capture of outcome data, to minimise the impact on busy clinical staff
- Conducting follow up phone calls to participants
- 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 and Pharmacy on at least a monthly basis

Models will encompass part time Research Midwives and variable Comprehensive Research Network (CRN) support. A site's participation in the trial will only be continued if pre-specified numbers of women have been recruited. The Midwife will be sent updates and newsletters, and will be invited to training and progress meetings approximately every six months.

4.4.4 Management of Sites

The TMG will actively manage recruitment and respond to fluctuations quickly by contacting the units directly. The (approximately) 30 iHOLDS Midwives will be supported by an external Lead Midwife who, together with the Chief Investigator and Senior 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 will be 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, for example mugs, pens, hand creams and light refreshments together with a monthly prize draw (£10) for Delivery Suites.

5. CONSENT

Summary:

- Participant Information Leaflet (PIL) to be given to woman as soon as possible after induction of labour is booked:
  - Induction may be booked in advance (PIL may initially be given at time of booking or posted by Research Midwife)
  - Decision to induce may be made immediately prior to the process starting
- **If the woman agrees, informed consent to be taken by Principal Investigator, Research Midwife, iHOLDS trained Obstetrician or iHOLDS trained Clinical Midwife (where local practice permits):**
  - **During the induction process prior to artificial membrane rupture (ARM)**
  - **Or at the point the decision is made to administer oxytocin**
- Eligibility to be confirmed by an iHOLDS trained Obstetrician
- Consent to be reconfirmed verbally if a period of time passes between written consent and randomisation to trial
- Randomisation to occur immediately prior to administration of oxytocin
- Process to be fully documented in medical notes

It will be the responsibility of the iHOLDS Principal Investigator, iHOLDS trained Obstetrician or Research Midwife to obtain written informed consent for each participant prior to performing any trial related procedure. iHOLDS trained Clinical Midwives will, where local practice allows, also be able to take informed consent. This responsibility will be delegated by the Principal Investigator (PI) as captured on the **Site Signature and Delegation Log** and local **iHOLDS Training Log**.

A **Participant Information Leaflet (PIL)** will be provided to facilitate this process. Investigators or delegate(s) will ensure that they adequately explain the aim, trial intervention, anticipated benefits and potential hazards of taking part in the trial to the participant. They will also stress that participation is voluntary and that the participant is free to refuse to take part and may withdraw from the trial at any time.

The participant will be given the PIL as soon as possible after their induction of labour is booked. This will enable them to read the PIL and to discuss their participation with others outside of the site research team. The participant will be given the opportunity to ask questions before signing and dating the latest version on the **Informed Consent Form (ICF)**. The participant must give explicit consent for the regulatory authorities, members of the research team and or representatives of the Sponsor to be given direct access to the participant's medical records.

For some women induction is booked in advance (1) and for others the decision is made immediately prior to the process starting (2).

1. **Induction booked in advance**: Research Midwives may send PIL's by post to women whose induction is booked in advance if time permits (at least 5 days until scheduled induction). When the woman is admitted for induction, a discussion regarding the trial will be had (as outlined above) and if the woman wishes to take part in the trial she will be asked to sign the ICF.

2. **Induction decision immediately prior to process starting:** Women undergoing induction will be given information (including the PIL) and a discussion take place during the period of time that cervical ripening is undertaken (cervix is opening and the membranes can be ruptured artificially), which for most women (either as an in or out patient) is 24 hours or more.
   Following this a decision is made as to whether oxytocin is prescribed and written informed consent for trial participation can be taken. If a period of time passes between the time of consent and the time of randomisation, consent will be reconfirmed verbally and should be documented in the medical notes.

The Investigator or delegate(s) and participant will then sign and date the ICF. Once the participant is entered into the trial, the participant's Trial Number will be entered on the ICF. A copy of the ICF will be given to the participant, a copy will be filed in the medical notes, and the original placed in the Investigator Site File (ISF). In addition, a copy of the ICF will be posted to the BCTU, with the participant's explicit consent, to monitor that the consent documentation has been completed correctly.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIL given to participant, version number of ICF signed, date consent received and date consent reconfirmed verbally (if required). A Documentation Label is provided to facilitate this. Where consent is obtained on the same day that the trial related assessments are due to start, a note should be made in the medical notes as to what time the consent was obtained and what time the procedures started.

Electronic copies of the PIL and ICF will be available from the iHOLDS Trial Office and will be individualised for each participating site including the relevant local institution header. With the participant's prior consent, their General Practitioner (GP) will be informed that they are taking part in the trial.

6. ENROLMENT AND RANDOMISATION

6.1 Enrolment and Screening

With appropriate training and where local practice allows, the Midwife caring for the woman can introduce the trial and answer any questions, take consent and randomise the woman, allocate the study medicines and then continue to look after the woman as care does not differ between the two study arms. The only difference is the dose regimen of oxytocin and allocation is blinded to participants, clinical staff and the Research Team. Confirming eligibility requires an iHOLDS trained Obstetrician, and these women would routinely be reviewed by an Obstetrician before oxytocin is prescribed which will facilitate this happening.

6.2 iHOLDS Recruitment Packs

The following iHOLDS recruitment packs will be supplied to sites for use during the study and copies should be stored on the Labour Ward and/or Maternity Suite at the convenience of the Midwives:

6.2.1 Information Pack

The Information Pack will contain all relevant documents to be used when approaching potentially eligible women regarding the study. One pack should be utilised per woman approached regarding the iHOLDS Trial. Information Packs will contain the following:

- Eligibility Criteria
- Participant Information Leaflet
- Suggested phrases for discussing the trial with potential participants
- Instructions and contact details for assistance

6.2.2 Labour Pack

The Labour Pack will contain all of the relevant documents to consent and enter a participant into the study, and all of the documents required during their participation in the study. One pack should be utilised per participant. Labour Packs will contain the following:

- Informed Consent Form
- Trial Entry Form
- Documentation label for medical notes (optional)
- Prescription stickers (optional)
- Labour Form
- iHOLDS oxytocin infusion regimens
- Repeat Treatment Form
- Instructions and contact details for assistance

6.3 Randomisation

6.3.1 Randomisation Methodology

Telephone randomisation will be available 24 hours a day through an automated secure system developed by the Health Services Research Unit at Aberdeen University. Also this system enables subsequent treatment packs of oxytocin to be allocated to the same women should they be required. 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:

- Gestation ≤38+6/40 weeks and ≥39/40 weeks
- Method used for cervical ripening: prostaglandin (prostin or propess) only/mechanical methods only/ both/none
- Cervical dilation <4 cm/≥4cm to <6cm/≥6cm
- 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.

6.3.2 Blinding

Double-blinded ampoules of oxytocin of high or standard dose will be provided for the trial (see *section 7.1 Intervention(s) and Schedule*). The blinding will be maintained throughout the trial.

6.3.3 Blinded Personnel

Participants, Investigators, Research Midwives/Nurses and other clinical staff will remain blind to the trial treatment allocation throughout the duration of the trial.

6.3.4 Allocation Concealment

Given the randomisation methodology described above, allocation concealment will be maintained throughout the trial.

6.3.5 Unblinding

Unblinding of participants as an emergency will not be required as the management of these women will not change in the light of this information. Any adverse event that occurs from whichever dose 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 recommended course of action regardless of randomised allocation.

Should unblinding be required, as part of any investigation, access to unblinding will be through the Trial Office who will be able to unblind during normal working hours. Unblinding at a site may trigger an additional monitoring visit in accordance with the iHOLDS Monitoring Plan.

6.3.6 Randomisation Process

After participant eligibility has been confirmed and informed consent has been received, the participant can be randomised into the trial.

Randomisation will be by telephone via an automated secure system developed by the Centre for Healthcare Randomised Trials (CHaRT) at the University of Aberdeen. Eligibility will be confirmed as part of the recruitment process and checked by the automated telephone randomisation system. It is anticipated that the task of randomising a woman will typically be delegated to a Midwife, but it can be conducted by an Obstetrician.

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. Full instructions are available on the **iHOLDS Trial Entry Form**.

6.3.7 Randomisation Records

Following randomisation, a confirmatory email will be sent to the randomiser, local Research Midwife, local PI, local Pharmacist, Chief Investigator and the iHOLDS Trial Office (iHOLDS@trials.bham.ac.uk).

Investigators will keep their own log which links participants with their allocated Trial Number in the **iHOLDS Participant Recruitment and Identification Log**. The Investigator must maintain this document, which is not for submission to the iHOLDS Trials Office. The iHOLDS Participant Recruitment and Identification Log should be held in strict confidence.

6.4 Informing Other Parties

If the participant has agreed, the participant's GP should be notified that they are taking part in the iHOLDS Trial, using the iHOLDS **GP Letter.**

7. TRIAL TREATMENT / INTERVENTION

7.1 Intervention(s) and Schedule

Synthetic oxytocin is manufactured by Mylan. Women randomised to the standard dose will receive a solution containing 2 x 5 iu ampoules made up to 50 or 500 mls of intravenous fluid and those randomised to the high dose, a solution containing 2 x 10 iu made up to 50 or 500 mls of intravenous fluid. Ampoules are manufactured as 5 and 10 iu, are cheap (<£1 per vial) and licensed for this specific use in pregnancy. The high dose regimen, if used at the higher infusion rates, is above the recommended maximum dose (shaded area in *Table 2* below).

There is currently national guidance about the standard dose regimen of oxytocin for women who are prescribed it as part of the induction process[1] but there is no accepted definition of a high dose regimen. We explored what high dose regimens were used for other licensed indications of oxytocin. In the Cochrane systematic review[2,3] which compared high versus low dose oxytocin regimens for women in delayed spontaneous labour, the authors defined high dose as a starting dose over 4 mU/minute and low dose as a starting dose of between 1 and 4 mU/minute with increasing increments at intervals ranging from every 15 to 40 minutes.

We have chosen to use regimens that fall within the ranges described within the Cochrane review, which minimise the escalation doses that are outside of the manufactures recommendations (shown in *Table 2* below) and that facilitate blinding as they match the increments of the standard dose regimen. We will therefore compare a high dose regimen of oxytocin (4 mU/min increasing every 30 minutes to a maximum of 64 mU/min) with a standard dose regimen (2 mU/min increasing every 30 minutes to a maximum 32 mU/min). The high dose regimen has a higher starting dose, earlier attainment of conventional maximum doses (at 2 hours rather than 4 hours) with the aim of the higher dose regimen being to achieve regular contractions more rapidly, rather than simply giving a higher total dose of oxytocin.

Table 2: **Treatment regimens proposed by iHOLDS**

	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 10iu in 50 or 500 mls*	*High strength 20iu in 50 or 500 mls*
0	*0.6*	*6*	*2*	*4*
30	*1.2*	*12*	*4*	*8*
60	*2.4*	*24*	*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*

Note: Doses in the shaded boxes are those outside of the national recommended regimen.

The standard dose regimen includes 2 ampoules of 5 iu oxytocin and the high dose 2 ampoules of 10 iu oxytocin diluted up to 50 mls or 500 mls with diluent (sodium chloride 0.9% or appropriate alternative) to ensure double blinding. As the total volume of both oxytocin ampoules is 2ml, 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 only manufactured in 5 and 10 iu concentrations which are similar in appearance, and treatment packs contain 2 ampoules and are stored in a fridge on the Delivery Suite. There are no differences between the current standard clinical care pathway and the pathway for those women randomised the high dose regimen, other than the concentration of the oxytocin. Doses in the shaded boxes of Table 2 are those outside the national recommended regimen.

7.2 Drug Interaction or Contraindications

7.2.1 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.
- Oxytocin must not be administered within 6 hours after vaginal prostaglandins have been given, or within 30 minutes of propess.

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.

There are no restrictions on breastfeeding for women recruited to the iHOLDS Trial.

7.2.2 Drug Interactions

7.2.2.1 Concomitant medication not recommended

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

Prostaglandins and their analogues

Prostaglandins and its analogues facilitate contraction of the myometrium hence oxytocin can potentiate the uterine action of prostaglandins and analogues and vice versa and a time period of 6 hours must be observed between prostaglandin use and administration of oxytocin.

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.

7.2.2.2 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.

7.3 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.

7.4 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 10* for further details). Oxytocin is given during labour and is not continued afterwards.

7.5 Treatment Supply and Storage

7.5.1 Treatment Supplies, Packaging and Labelling

Oxytocin is produced by Mylan and will be purchased by the Sponsor. Sharp Clinical Services are a leading provider of clinical supply chain services and licensed by the Medicines and Healthcare products Regulatory Agency (MHRA). Sharp Clinical Services will be responsible for the blinding, labelling, packaging and distribution of the study drugs.

7.5.1.1 CHaRT Pack Management System for Oxytocin

Telephone randomisation will be available 24 hours a day through an automated secure system developed by the Centre for Healthcare Randomised Trials (CHaRT) at the Health Services Research Unit at Aberdeen University. Also this system enables subsequent treatment packs to be allocated to the same women should they be required. 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 variables listed in *Section 6.3.1*.

7.5.2 Drug Storage, Temperature control and Management

The iHOLDS IMP is stored in a fridge (ideally the routine Drug Fridge) and must be stored between 2-8^{o}C as stated in the SPC, however the IMP can be stored up to 30^{o}C for a maximum of three months, after which time it must be discarded.

Fridge temperatures must be continuously monitored and daily readings of the maximum/minimum must be recorded. Temperature deviations will not be considered a protocol deviation but strict IMP management processes are in place. Once made up the expiry time for the infusion is 24 hours.

As a pragmatic trial an online pack managment system will capture temperature deviations for the IMP stock at sites. Where temperatures are above 8 °C and below 30 °C (minor temperature deviation) the shelf life of the IMP will be limited to 3 months (in line with SPC). Where temperatures drop below 2 °C or exceed 30 °C (major temperature deviation), the IMP will be quarrantined and scheduled for destruction. Both categories of temperature deviation will be reported to the iHOLDS Trial Office by site staff via the online pack management system and/or a **Temperature Deviation Form** in an expedited fashion, to best minimise temperature deviations within the trial. Further details, including IMP destruction processes, are provided in the **IMP Manual**.

Participating sites 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 but may be recorded on paper initially. Temperature of 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.

Buffered thermometers are supplied to sites by the iHOLDS Trial Office for use in the study. The buffered thermometers are set up to alarm if there is a major temperature deviation and the temperature is recorded < 2°C or ≥ 30°C (where there is no stability data) so we have also set up a system where the clinical staff phone the 24/7 telephone randomisation system to halt recruitment in the site should that occur.

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. 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.

7.6 Accountability and Compliance Procedures

7.6.1 Compliance

Compliance is presumed since the trial drug is titrated via an intravenous infusion and stopped when the baby is born. Rarely the woman may not receive the allocated treatment before she gives birth and this should be recorded on the Case Report Form (CRF), as should the number of mls of oxytocin received.

7.6.2 Accountability

The IMP will be stored in Pharmacy upon delivery to site. In order to allocate IMP to the Labour Ward, Pharmacy will access the web based system and state how many treatment packs are required for transfer. Further details about this are provided in the IMP Manual.

Please note; IMP must not be placed on the Labour Ward UNLESS they have been allocated by the web based system as they will not be recognised as available for randomisation.

7.6.2.1 Stock held on Delivery Suite

The IMP must be segregated from other stock in the fridge. The designated storage area must be labelled "iHOLDS Trial stock for clinical trial use only". Please note; storage must allow for air flow around the IMP within the fridge.

The delegated Clinical Trial Pharmacist at site is responsible for the storage of the IMP. The site iHOLDS Midwife is responsible for requesting the IMP and restocking the Labour Ward.

iHOLDS Trial documentation is supplied for use at site, however sites own documentation may be used upon prior approval from the iHOLDS Trial Office.

8. OUTCOME MEASURES AND STUDY PROCEDURES

We will collect data to assess important maternal and neonatal clinical outcomes, to provide quantitative measurement of women's experiences of labour, birth and the early postnatal period two weeks after birth using a questionnaire containing a validated tool, and to compare the costs associated with the higher dose regimen of oxytocin with those of the standard dose. These include the core outcomes related to this question from those recently published for induction of labour trials[24].

Eligibility will be confirmed as part of the recruitment process and checked by the automated telephone randomisation system. Baseline data will include reason for induction; gestation at induction and cervical dilation at randomisation, as well as induction agents used to that point. Data collection during labour is minimal, to encourage engagement from clinical staff, with the majority of maternal and neonatal data being collected before discharge from hospital, which is usually within a couple of days of birth. Should the baby be admitted to the Neonatal Unit an additional form is completed detailing care.

Data collected will include those necessary for pharmacovigilance as oxytocin has a list of possible events related to use which are listed in the Summary of Product Characteristics produced by the manufacturers (Mylan). Training of staff and clear recording of all these events developed during the iHOLDS Trial will facilitate the timely reporting of these to the Trial Office, and if required to the DMC and regulatory authorities.

8.1 Measurement of Maternal Psychological Health

A recent systematic review to identify outcome measures in randomised trials measuring effectiveness of oxytocin for treatment of delay in the first and second stages of labour and to identify any positive health-focussed outcomes[25] found outcomes used are heterogeneous and tend to focus on adverse events. They recommended that in future randomised trials of oxytocin use in labour, women-centred and health-focussed outcome measures should be included, which may instil a more salutogenic culture in childbirth. Further follow up was also requested by the women undergoing induction who were asked about the trial as part of our work to develop the trial.

Women will be given the options of mobile phone, email or postal response to the questionnaire.

Each participant will receive the initial questionnaire and one reminder by their preferred method. The final contact will be attempted by a telephone call from the site Midwife to complete the questionnaire.

All women who have access to smart phone technology, agree that mobile phone contact is the preference and who provide a contact number will be sent a questionnaire using mobile phone technology two weeks after birth containing a validated tool to explore satisfaction with care and the experience of labour and birth (the Birth Satisfaction Scale- Revised Indicator (BSS-RI))[19]. For those women who choose to have the questionnaire sent by post, postal reminders will be sent from iHOLDS Trial Office. We will employ evidence based methods[26], to maximise response rates and will include a £5 Amazon Shopping Voucher. One reminder will be sent in each instance and where no response is obtained, this will be followed by a phone call from the participating site to complete the questionnaire over the phone.

Contact will be by text message or online through TextLocal (www.textlocal.com), or by post or by phone, depending on the participant's preference.

In order for Textlocal to contact the participant, Textlocal will be sent the woman's mobile telephone number. So that we can link the responses given by the woman back to her record on the study database Textlocal will also be given the woman's study number. No other information about the participant or her baby will be given to Textlocal. The woman's study number, telephone number and responses will be encrypted whilst being stored by Textlocal, and these data will not used by Textlocal for any other purpose. Once the responses have been transferred from Textlocal to the study database held at the University of Birmingham, Textlocal will securely delete all of the study data that they hold.

8.2 Cost Comparison

The costs associated with the higher dose regimen of oxytocin will be compared with the current standard regimen. If a higher starting dose is effective in reducing the rate of caesarean section, then there may be important cost implications for the health care sector. The cost comparison is necessary to assess whether a higher starting dose will be deliverable within the NHS, given current budgets. Cost considerations are a core concern for clinical staff and providers and alternative interventions are unlikely to be adopted unless there is evidence about their costs compared to usual care.

The primary objective of the trial is to determine the effectiveness of a higher dose regimen of oxytocin compared with the current standard dose, and so the economic analysis will focus on whether there is a difference in costs associated with these doses. An NHS/PSS perspective will be adopted in line with NICE recommendations[27] .

An advantage of the data required for this trial is that the majority are routinely collected and trial participation is relatively brief so clinical outcomes are unlikely to be lost. This is because women are recruited during induction of labour and the majority of data relates to birth outcomes (including the primary outcome of CS) prior to discharge from the Maternity Unit. Outcome data entry will be through a web-based portal, which will include consistency and validation checks and a similar one is already developed, tested and in use for the HOLDS trial.

8.3 Pilot Stage Outcomes

Pilot stage objectives are detailed in *Section 2.1*.

8.4 Main Trial Outcomes

8.4.1 Primary Outcome

- Caesarean section

8.4.2 Secondary Outcomes

8.4.2.1 Maternal

- Epidural use during labour and birth
- Duration of the stages of labour:
    - Second (from full dilation to the birth of the baby) and
    - Third (is the time from the birth of the baby to the expulsion of the placenta and membranes).
- Time from randomisation to birth [minutes]
- Time from induction of labour (induction of labour is defined as the process by which labour is started prior to its spontaneous onset by progressive cervical effacement and dilatation and/or artificial stimulation of uterine contractions, leading to active labour and birth)
- Mode of birth (spontaneous vaginal birth (SVB), instrumental or CS)
- Degree of perineal trauma (first, second, third and fourth degree):
    - First degree – injury to skin only
    - Second degree – injury to the perineal muscles but not the anal sphincter
    - Third degree – injury to the perineum involving the anal sphincter complex:
        - 3a – less than 50% of external anal sphincter thickness torn
        - 3b – more than 50% of external anal sphincter thickness torn
        - 3c – internal anal sphincter torn
    - Fourth degree – injury to the perineum involving the anal sphincter complex (external and internal anal sphincter) and anal epithelium.
- Reason for and grade of CS;
    - 1. immediate threat to the life of the woman or fetus
    - 2. maternal or fetal compromise which is not immediately life-threatening
    - 3. no maternal or fetal compromise but needs early delivery
    - 4. delivery timed to suit woman or staff.

- Confirmed urinary retention requiring catheterisation
- 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 ST analysis (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 maternal serious morbidity (anaphylaxis, cardio- respiratory arrest, stroke, pulmonary oedema/ embolus, hyponatremia, postpartum haemorrhage, shoulder dystocia, chorioamnionitis, uterine rupture/hysterectomy)
- Active management of third stage of labour
- Length of time after birth in hospital [days]
- Admission to HDU and/ or ITU
- Maternal death.

Measurement of maternal psychological health. A validated tool to explore satisfaction with care and the experience of labour and birth (the Birth Satisfaction Scale- Revised Indicator (BSS-RI))[19] will be collected two weeks after birth. This will be collected from the women as a questionnaire.

8.4.2.2 Process

Time from randomisation to commencement of allocation [minutes]:

- Total oxytocin dose [International units: IU]
- Time to maximum oxytocin rate [minutes]
- Maximum oxytocin dose reached

8.4.2.3 Neonatal

- Birthweight
- Apgar score at 5 minutes
- Venous and arterial cord blood gases when collected (PH)
- Need for resuscitation
- Breastfeeding on discharge from hospital
- Length of time after birth in hospital [days]
- Birth trauma (brachial plexus injury, fractured clavicle)
- Need for neonatal review on ward (excluding routine baby check)
- Use of any antibiotics
- Jaundice requiring phototherapy and/ or transfusion
- Need for admission to Neonatal Unit (NNU) and
- Level of Neonatal Unit care received (level 1,2,3) including Intensive Care
- Duration of respiratory support [days]
- Days to full oral feeds
- Meconium aspiration syndrome
- Seizures
- Neonatal encephalopathy (SARNAT grade)
- Therapeutic hypothermia (cooling)
- Intrapartum stillbirth
- Early neonatal death (within seven days of birth).

8.4.3 Cost Attribution

8.4.3.1 Collection of Cost Data

NHS resource use and costs for women and infants will be collected prospectively in both arms via the Case Report Form (CRF). This will include the costs associated with: i) giving the allocated dose of oxytocin by intravenous infusion; ii) maternal and fetal monitoring and titration of the dose; iii) delivery; iv) length and type of hospital inpatient stay (any adverse events will affect the length and type of hospital stay); v) any other NHS resource use for the woman and infant. Unit costs will be obtained and attached to resource items in order that a cost can be calculated for each patient. Unit costs will be obtained from published sources and centers participating in the trial. Published sources will include Unit Costs of Health and Social Care[20] and NHS Reference Costs[21]. Costs used in other relevant published sources will be sought for use in the sensitivity analyses.

8.5 Schedule of Assessments

Table 3: Schedule of Assessments table

		Pre-enrolment	Enrolment	Allocation	Intervention			Outcome	
	TIMEPOINT	***Induction clinic visit***	***At admission***	***Following membrane rupture when oxytocin prescribed***	***Oxytocin Administration***	***Birth***	***Discharge***	***Follow Up***	***2 weeks after birth***
ENROLMENT	**PIL provided**	X	X						
	Eligibility screen	X	X	X					
	Informed consent		X	X					
	Randomisation			X					
INTERVENTION	**High Dose**				X				
	Low Dose				X				
	Intervention end					X			
ASSESSMENTS	**Baseline data collection**			X					
	Treatment data collection				X				
	Birth and discharge outcome data collection					X	X	X	
	Neonatal data collection if admitted to NNU						X	X	
	SAEs/SUSARs				X	X	X		
	Maternal satisfaction								X

9. PATIENT AND PUBLIC INVOLVEMENT AND ENGAGEMENT (PPIE)

Ultimately the aim of Patient and Public Involvement (PPI) engagement is to undertake research 'with women' and not 'on women', to develop a trial that is acceptable to women undergoing induction of labour and to ensure that we assess whether high dose regimens of oxytocin do reduce the rate of CS. Induction of labour is a relatively common occurrence for women, and having insight into the user perspective has been, and will continue to be, central to the trial development and delivery.

A dedicated PPI representative has been involved at every stage of the development of this trial, and this will continue to be integral to every phase of trial development and delivery. There is also PPI involvement on our TSC.

Recruiting women in these circumstances can sometimes be challenging and we plan to use a process that follows national recommendations[21] regarding obtaining informed consent to participate in perinatal research where consent is time critical and ensure women are given information as soon as their induction is booked to enable them sufficient time to make an informed decision. We realise the importance of training staff so they can explain the study and answer any questions. To ensure women have information before the induction process begins we will make sure:

- A discussion takes place when the induction is booked and information is given or sent to the women at that time, which includes a **Participant Information Leaflet**.
- That information is given as part of the induction process. Most women are seen (either as an in or out patient) for 24 hours or more during cervical ripening and it is during this period that information (including the PIL) will be given and a discussion take place.

If at some point they become eligible (i.e. oxytocin is being prescribed as part of the induction process) the women will be asked to consent to participate in the trial and subsequently randomised to either high or standard dose regime.

We believe that the plans we have will give time for women to read the information and ask any questions they may have. We have asked women undergoing induction of labour in eleven of the HOLDS units and they felt this would be acceptable. Patient and public involvement and engagement has been integral in forming this process.

We have consulted women undergoing induction in the development of the trial and will actively consult women through selected Maternity Units, before recruitment begins, as the trial progresses and at the end of the trial. These discussions will be hosted by a dedicated PPI representative and will ensure that the information we provide for women at each stage is clear and understandable. In these discussions we will include the processes that we use to distribute information about the trial and the approach to women, the methods we use to distribute the follow-up questionnaire and how we might describe the results. This will mean that how we describe the trial at each point will be clear and understandable, that when and how women are approached is appropriate, which is likely to improve recruitment. What women tell us in these discussions is also likely to maximise response rates to the follow-up questionnaire and to ensure that the results are written clearly and are widely disseminated.

Using social media (both Twitter and a planned designated Facebook page) we will engage more broadly with women undergoing induction of labour. We believe these plans will not only ensure women are at the heart of what we do but are also likely to improve recruitment, retention and dissemination.

10. PARTICIPANT WITHDRAWAL AND CHANGES OF STATUS WITHIN 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 and maternal satisfaction data) will still be collected and reported to the iHOLDS Trial Office, unless they explicitly state their intention to withdraw from all aspects of the trial.

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 iHOLDS trial as there would be no further procedures or tests required for the trial.

11. ADVERSE EVENT REPORTING

11.1 Definitions

Table 4: Adverse Event Definitions

Adverse Event	AE	Any untoward medical occurrence in a participant or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Adverse Reaction	AR	All untoward and unintended responses to an IMP related to any dose administered.
Serious Adverse Event	SAE	Any untoward medical occurrence or effect that: • Results in death or is life-threatening* • Requires hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • Is a congenital anomaly/birth defect** • Or is otherwise considered medically significant by the Investigator***
Serious Adverse Reaction	SAR	An Adverse Reaction which also meets the definition of a Serious Adverse Event
Unexpected Adverse Reaction	UAR	An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product). When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.
Suspected Unexpected Serious Adverse Reaction	SUSAR	A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information. A SUSAR should meet the definition of an AR, UAR and SAR.

*Life-threatening in the definition of a serious adverse event refers to an event in which the mother/fetus/infant 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.

**The definition of a Serious Adverse Reaction (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 reportable as a SAR or SAE.

***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.

11.2 Adverse Event General Recording Requirements

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). Definitions of different types of AEs are listed in *Section 11.1 Definitions* above.

The Investigator should document all AEs experienced by the trial participant in the source data and assess the seriousness and causality (relatedness) 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 iHOLDS 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.

11.3 Adverse Events (AE) Reporting

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

Labour outcomes

- Uterine tachysystole (defined as greater than 5 contractions in 10 minutes for a period of 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)

Maternal outcomes

- Headache
- Nausea
- Vomiting
- Tachycardia or bradycardia

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 11.4* below).

11.4 Serious Adverse Advents (SAE) Reporting

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

Table 5: iHOLDS SAE Reporting Requirements

SAE category	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 11.4.1* 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 11.4.2* 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.

11.4.1 Events that require **expedited** reporting to the BCTU on the SAE Form

All SAEs (except those listed in *Section 11.4.2*) 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 4*, the following events (listed for convenience, but are not limited) should be reported on an **SAE Form**:

Maternal outcomes

- Maternal anaphylaxis, cardio respiratory arrest, stroke
- Maternal hyponatremia
- 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
- 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.

11.4.2 Events that do not require reporting to 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):

Expected SAEs for prolonged hospital stays

These include prolonged hospital stays for the following reasons:

- For baby due to 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.

11.5 SAE reporting process

11.5.1 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 **iHOLDS 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: iHOLDS@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. If 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. 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 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.

11.5.2 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.

11.6 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 6: 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.

11.7 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 7: 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 relevantly qualified 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 4* 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 both parties will be documented, and where the event requires further reporting, this will be provided with the report.

11.8 Assessment of Expectedness by the CI

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

Table 8: 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 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 11.10)*.

11.9 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.

11.10 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.

11.11 Urgent Safety Measures

If any urgent safety measures are taken, the BCTU shall 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.

11.12 Monitoring pregnancies for potential SAEs

Since live birth is an outcome in the trial, congenital anomalies or birth defects will be routinely monitored during the trial. Considering 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.

12. DATA HANDLING AND RECORD KEEPING

12.1 Source Data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of the subject, source data will be accessible and maintained.

Table 9: Source data definitions and examples

Data	Source
Participant Reported Outcomes (Maternal Satisfaction Questionnaire)	The original participant-completed CRF is the source and will either be: 1.Kept with the participant's trial record at site, where completed over the phone and copies posted to the iHOLDS Trial Office 2. Kept at the iHOLDS Trial Office where the postal questionnaire is returned to the Trial Office directly 3. The original record of the questionnaire completion is the source. It is held on Textlocal and BCTU servers as part of the mobile phone enabled questionnaire completion.
Clinical event data	The original clinical annotation is the source document. This may be found on clinical correspondence, or electronic or paper participant records. Clinical events reported by the participant, either in or out of clinic (e.g. phone calls), must be documented in the source documents. This includes the **iHOLDS Labour Form** which should remain part of the participant's medical records after being transcribed to the CRFs.
Recruitment	The original record of the randomisation is the source. It is held on the University of Aberdeen and BCTU servers as part of the randomisation and data entry system.
Drop out	Where a participant expresses a wish to withdraw, the conversation must be recorded in the source documents.

12.2 Case Report Form (CRF) Completion

A set of CRFs is required and should be completed for each individual subject. The data held on the completed original CRFs are the sole property of the respective PIs whilst the data set as a whole is the property of the Sponsor and should not be made available in any form to third parties except for authorised representatives or appropriate regulatory authorities, without written permission from the Sponsor. Appropriate data sharing requests will be considered by the Sponsor.

The **iHOLDS Site Signature & Delegation Log** will identify all those personnel with responsibilities for data collection. CRFs will be completed on the electronic CRF (eCRF). The CRFs will comprise (but will NOT be limited to) the following forms:

Table 10: Case Report Form schedule

Form Name	Schedule for submission
Informed Consent Form	Prior to or at the point of randomisation or earlier as described in S*ection 3.3 Identification of Participants.* Copy to be sent by post to the iHOLDS Trial Office following randomisation if the patient gives explicit consent (see S*ection 5 CONSENT*)
Trial Entry Form	Confirmation of eligibility by an Obstetrician and automated telephone randomisation service Trial Entry Form to be returned by post to the Trial Office within 5-10 days of randomisation
Birth and Discharge Form	Electronic completion within 5-10 days of randomisation
Neonatal Form	Completed electronically only for those babies who are admitted to NNU Electronic completion within 5-10 days of the end of care episode
Maternal Satisfaction Questionnaire	Email reminder, text message or paper questionnaire to be sent to the participant, with final chase being a phone call from the centre based Research Midwife. See S*ection 0* below for more details
Serious Adverse Event Form	Emailed 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 to the Trial Office on discovery via a **Deviation Form**.

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.

12.3 eCRFs

Staff delegated to complete eCRFs will receive training for online completion of the eCRFs in the trial database from source data. Online data entry is achieved via unique passwords and usernames which must not be shared amongst the team. All time formats, where applicable, should be in accordance with the 24 hour clock. Rounding of numbers, where applicable, should be in the normal way (i.e. ≥*x*.5 is rounded up to the nearest whole number). Laboratory test data that is used to inform clinical decisions should always be supplied. If a test is repeated it is either to confirm or clarify a previous reading. Confirmatory tests should use the original test values.

12.4 Participant completed Questionnaires

The Maternal Satisfaction Questionnaire, which explores satisfaction with care and the experience of labour and birth, will be completed by the participant. At the time of randomisation the participant will express their preference for contact to receive the questionnaire, be that by smartphone, post or email. Each participant will then be contacted by their preferred method. One reminder will follow before the site Midwife will attempt to call the participant and complete the questionnaire by phone.

12.5 Data Management

12.5.1 Data Entry

Data entry will be completed by site staff from source data via a bespoke built BCTU trial database. The data capture system will conduct automatic range checks for specific data values to ensure high levels of data quality. Queries (or Data Clarification Forms [DCFs]) on the trial data will be raised using the integrated data query system in the trial database, with the expectation that these queries will be completed by the site within 30 days of receipt. Overdue data entry and data queries will be requested on at least a monthly basis.

12.5.2 Longer Term Follow-Up

Consent will be obtained from women to contact them in the future requesting additional (optional) consent for longer term follow-up (including data on their babies) should it be required. This optional consent will allow us to contact women requesting consent for linkage to patient data available in NHS routine clinical datasets, including primary care data (e.g. Clinical Practice Research Datalink, The Health Improvement Network, Q Research), secondary care data (Hospital Episode Statistics) and mortality data from the Office of National Statistics through NHS Digital and other central UK NHS bodies. If they agree, the participant will consent to the trial team sending their name, address, date of birth and NHS number to the relevant national registry and then for the national registry to link this to their data and send the information back to the trial team. The consent will also allow access to other new central UK NHS databases that will appear in the future.

12.5.3 Coordinating Centre Data Management

Processes will be employed to facilitate the accuracy of the data included in the final report. These processes will be detailed in the trial specific Data Management Plan. Coding and validation will be agreed and will be signed off once the implementation of these has been assured.

12.5.4 Summary of Data Collection Points, Personnel and Training Requirements

All clinical staff working on the study will receive iHOLDS 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 iHOLDS 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 11: Personnel and training requirements

Process	Time	CRF	Person responsible
Approach potentially eligible women	When induction is booked or after admission for induction	None	iHOLDS trained Obstetrician or Midwife
Consent	Following initial check of eligibility	Informed Consent Form	iHOLDS trained Obstetrician or Midwife
Eligibility	Following confirmation of decision to use oxytocin	Trial Entry Form	iHOLDS trained Obstetrician
Randomisation telephone call	Following confirmation of consent and eligibility	Complete Trial Entry Form	iHOLDS trained Obstetrician or Midwife
Prescription of drug	Following randomisation	Prescription chart	iHOLDS trained Obstetrician
Study treatment administration	Following prescription of drug	Labour Form	iHOLDS trained Midwife or Obstetrician
Labour data collection	From commencement of study treatment until after birth	Labour Form	iHOLDS trained Midwife
Birth outcome data collection	After discharge	Birth and Discharge Form	Site iHOLDS Midwife with NIHR GCP training
Maternal Satisfaction	After discharge	Maternal Satisfaction Questionnaire	Site iHOLDS Midwife with NIHR GCP training
SAE reporting Determination of Causality of SAE	When they occur	SAE Form	Site iHOLDS Midwife with NIHR GCP training Site PI (or medically qualified delegate) with NIHR GCP training

12.6 Data Security

The security of the System is governed by the policies of the Universities of Birmingham and Aberdeen. The respective University's Data Protection Policy and the Conditions of Use of Computing and Network Facilities set out the security arrangements under which sensitive data should be processed and stored. All studies at the Universities of Birmingham and Aberdeen have to be registered with the Data Protection Officer and data held in accordance with the Data Protection Act. The University will designate a Data Protection Officer upon registration of the study. The Study Centre has arrangements in place for the secure storage and processing of the study data which comply with the University of Birmingham policies.

The System incorporates the following security countermeasures:

- Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.
- Logical measures for access control and privilege management: including restricted accessibility, access controlled servers, separate controls used non-identifiable data etc.

- Network security measures: including site firewalls, antivirus software, separate secure network protected hosting etc.
- System Management: the System shall be developed by the BCTU Programming Team and will be implemented and maintained by the BCTU Programming Team.
- System Design: the system shall comprise of a database and a data entry application with firewalls, restricted access, encryption and role based security controls.
- Operational Processes: the data will be processed and stored within the Study Centre (University of Birmingham).
- Data processing: Statisticians will have access to anonymised data.
- System Audit: The System shall benefit from the following internal/external audit arrangements:
    - Internal audit of the system
    - Periodic IT risk assessments
- Data Protection Registration: The University of Birmingham has Data Protection Registration to cover the purposes of analysis and for the classes of data requested. The University's Data Protection Registration number is Z6195856.

12.7 Archiving

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g. signed ICFs, Investigator Site Files, Pharmacy Files, participants' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 25 years.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Site Set-up and Initiation

All PIs will be asked to sign the necessary agreements including a **Clinical Study Site Agreement** between the PI and the Sponsor, and supply a current CV and GCP certificate to BCTU. All site staff who are performing trial specific tasks are required to sign the **Site Signature and Delegation Log** and/or local **Training Log**, which details which tasks have been delegated to them by the PI.

Prior to commencing recruitment, each recruiting site will undergo a process of initiation, either a meeting or a teleconference, at which key members of the site research team are required to attend, covering aspects of the trial design including: protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File and a Pharmacy File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The BCTU Trials Team must be informed immediately of any change in the site Research Team.

Additional training will be delivered to clinical staff (Clinical Midwives and Obstetricians) working on the study either by the site Research Midwife, or the BCTU via an online training platform. This training includes aspects of GCP relevant to their role within the study. Attendance is documented on the Training Log and signed off by the PI to confirm delegation of duties.

13.2 Monitoring

The monitoring requirements for this trial have been developed following trial specific risk assessment by the Sponsor and as documented in the Monitoring Plan.

13.2.1 Onsite Monitoring

For this trial we will monitor sites in accordance with the trial Risk Assessment and Monitoring Plan. Any monitoring activities will be reported to the Trials Team and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, high or low SAE reporting rates, excessive number of participant withdrawals or deviations (also defined in the Monitoring Plan). Investigators will allow the iHOLDS Trial staff access to source documents as requested. The monitoring will be conducted by BWCNFT.

13.2.2 Central Monitoring

Trials staff will check incoming ICFs and CRFs for compliance with the protocol, data consistency, missing data and timing at a frequency and intensity determined by the Data Management Plan. Sites will be sent **Data Clarification Forms** (DCFs) requesting missing data or clarification of inconsistencies or discrepancies.

13.3 Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents. The Investigator will comply with these visits and any required follow up. Sites are also requested to notify BCTU of any relevant inspections.

13.4 Notification of Serious Breaches

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified may be reported to the Trial Management Group, Trial Steering Committee, and the REC. This includes reporting serious breaches of GCP and/or the trial protocol to the Research Ethics Committee (REC) and Medicines and Healthcare products Regulatory Agency (MHRA).

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.

For the purposes of this regulation, a “serious breach” is a breach which is likely to affect;

- The safety or physical or mental integrity of the subjects of the trial
- The scientific value of the trial

Sites are therefore requested to notify the iHOLDS Trial Office of any suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trial Office is investigating whether or not a serious breach has occurred, sites are also requested to cooperate with the Trial Office in providing sufficient information to report the breach to the MHRA where required, and in undertaking any corrective and/or preventive action.

14. END OF TRIAL DEFINITION

For the participants, the end of trial is defined as eight weeks after birth to allow for the collection of follow up data. This will allow sufficient time for the completion of protocol procedures, data collection and data input.

The end of trial is defined as six months after the date of last data capture and following resolution of all data queries relating to critical data items. The iHOLDS Trial Team will notify the main REC, MHRA and external Sponsor within 90 days of the end of trial. Where the trial has terminated early, the Trial Office will inform the MHRA and REC within 15 days of the end of trial. The iHOLDS Trial Office will provide them with a summary of the clinical trial report within 12 months of the end of trial. A copy of the end of trial notification as well as the summary report will be sent to MHRA and REC.

15. STATISTICAL CONSIDERATIONS

15.1 Sample Size

The sample size will be 2400 women, allowing 90% power (p=0.05) to detect an absolute risk reduction of 6% (equivalent to a 20% relative reduction), assuming the rate of caesarean section in the standard-regimen group to be 30%. This includes an approximate 4% inflation for any loss to follow-up or withdrawals.

The rate of 30% in the standard-regimen group is taken from our survey of 22 Obstetric Units (including data on over 2500 women) currently recruiting to another intrapartum trial (the HOLDS trial). In the same survey, Obstetricians indicated that a minimally important absolute reduction of 6% in caesarean section rate would be enough for them to change practice from standard dose oxytocin to a high dose regimen. The 4% inflation for any loss to follow-up or withdrawals is considered conservative given the very low rate of missing outcome data in a similar pilot study we conducted[28].

15.2 Analysis of Outcome Measures

A separate Statistical Analysis Plan (SAP) will provide a more comprehensive description of the planned statistical analyses. A brief outline of these analyses is given below:

The primary comparison groups will be composed of those treated with the high dose regimen of oxytocin versus those treated with standard dose regimen. In the first instance, all analyses will be based on the intention to treat principle, i.e. all participants will be analysed in the treatment group to which they were randomised irrespective of compliance or other protocol deviation. For all major outcome measures, summary statistics and differences between groups, e.g. relative risks, will be presented with 95% confidence intervals. For the primary outcome, a p-value from a two-sided test will also be produced. All outcomes will be adjusted for the minimisation variables listed in *Section 6.3* where possible.

For secondary outcomes, no adjustment for multiple comparisons will be made and hence significance should not be inferred from the confidence interval width. Safety outcomes (e.g. SAEs – full list to be defined in the SAP) may be subject to statistical testing without adjustment for multiple testing, as adjustment for multiplicity is counterproductive for considerations of safety[28].

15.2.1 Primary Outcome Measure

We will use a log-binomial regression model to calculate the relative risk and 95% confidence of the primary outcome (caesarean section). Minimisation variables will be included as covariates. The p-value from the associated chi-squared test will be produced and used to determine statistical significance.

15.2.2 Secondary Outcome Measures

Relative risks and 95% confidence intervals for dichotomous secondary outcomes (e.g. vaginal birth, tachysystole) will be generated in the same fashion as the primary outcome. P-values will not be reported. Linear regression will be used for continuous data (e.g. birthweight) to produce adjusted mean differences and a Cox Proportional Hazard (PH) model (provided the assumptions of proportionality are met) for time to event data (e.g. time from randomisation to birth). Hazard ratios will be generated here.

15.2.3 Subgroup Analyses

Subgroup analyses will be undertaken on the same variables used as the minimisation variables (apart from centre). Tests for statistical heterogeneity (e.g. by including treatment group by subgroup interaction parameter in the regression model) will be performed alongside examination of effect estimate within subgroups.

15.2.4 Missing Data and Sensitivity Analyses

Every attempt will be made to collect full follow-up data on all study participants; it is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. This will include imputing missing data using multiple imputation techniques. Full details will be included in the Statistical Analysis Plan.

15.3 Planned Interim Analysis

Interim analyses of safety and efficacy for presentation to the independent DMC will take place during the study. The committee will meet prior to study commencement to agree the manner and timing of such analyses but this is likely to include the analysis of the primary and major secondary outcomes and full assessment of safety (SAEs) at least at annual intervals. Criteria for stopping or modifying the study based on this information will be ratified by the DMC. Details of the agreed plan will be written into the Statistical Analysis Plan. Further details of DMC arrangements are given in S*ection 16.5 Data Monitoring Committee*.

15.4 Planned Final Analyses

The primary analysis for the study will occur once final follow up (Maternal Satisfaction Questionnaire) is complete and corresponding outcome data have been entered onto the study database and validated as being ready for analysis.

15.5 Health economic evaluation

15.5.1 Analysis for the cost comparison:

The cost analysis is deliberately simple to be in accordance with the Commissioning Brief. Given the objectives of the trial, only a within trial cost comparison will be carried out. The analysis will initially compare all costs and outcomes for the intervention and for the standard dose regimen in a disaggregated format. The main analysis will adopt an incremental approach to concentrate on comparing resource use and costs between trial arms and an overall cost per patient will be calculated. A simple cost-consequences analysis will also be reported, to compare costs and the important consequences as assessed in the trial[29]. We have included the recently published core outcome set in our data collection[24].

As the majority of cost data are skewed, and the mean cost associated with the different doses is of importance, a bootstrapping approach will be undertaken in order to calculate confidence intervals around the mean costs. We will use both simple and probabilistic sensitivity analyses to explore the robustness of the results to plausible variations in key assumptions[30]. The sensitivity analyses will allow us to explore key drivers of costs and we will also assess the generalisability of the results to other settings.

16. TRIAL ORGANISATIONAL STRUCTURE

16.1 Sponsor

The Sponsor for this trial is Birmingham Women's and Children's NHS Foundation Trust (BWCNFT or BWH).

16.2 Coordinating Centre

The trial coordinating centre (Trial Office) is Birmingham Clinical Trials Unit (BCTU), based at the University of Birmingham.

16.3 Trial Management Group

The Trial Management Group will take responsibility for the day-to-day management of the trial, and will include (but is not limited to) the CI, Statistician, Senior Trial Manager, Sponsor representative and Lead Midwife. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. A full list of TMG members is available in the protocol *Section Administrative Information.*

16.4 Trial Steering Committee

A single TSC will be created for the iHOLDS Trial and meet via teleconference, or in person, as required depending on the needs of the trial and at least once per year.

Membership and duties/responsibilities are outlined in the TSC Charter. In summary, the TSC will: provide overall oversight of the trial, including the practical aspects of the study, as well as ensuring that the study is run in a way which is both safe for the participants and provides appropriate feasibility data to the Sponsor and Investigators. The TSC have a role in ensuring scientific credibility of the study and will act as appropriate, upon the recommendations of the DMC, carrying responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy. A full list of TSC members is available in the protocol *Section Administrative Information*.

16.5 Data Monitoring Committee

Data analyses will be supplied in confidence to an independent Data Monitoring Committee (DMC), which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants. The DMC will operate in accordance with a trial specific charter. The DMC will meet at least annually as agreed by the Committee and documented in the Charter. More frequent meetings may be required for a specific reason (e.g. safety). Should a maternal death, neonatal death, neonatal encephalopathy or any other serious safety issue be identified, each instance will be reported promptly to the DMC and an emergency meeting convened if required.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise participant safety. The trial will stop early if the interim analyses showed differences between treatments that were deemed to be convincing to the clinical community. A full list of DMC members is available in the protocol *Section Administrative Information*.

16.6 Finance

The research costs of the trial are funded by a National Institute for Health Research (NIHR) Health Technology Assessment (HTA), reference 17/137/02, awarded to Professor Sara Kenyon at the Birmingham Women's and Children's NHS Foundation Trust. The trial has been designed to minimise extra 'service support' costs for participating hospitals as far as possible. 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).

17. 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 iHOLDS Trials Team, site initiation training is complete and the iHOLDS Trial Team 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.

18. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the General Data Protection Regulation, 2018.

Participants will always be identified using their unique trial identification number and initials on the Case Report Form and any correspondence between members of the BCTU and the site Research Team. Participants will give their explicit consent for the movement of their **Informed Consent Form**, giving permission for BCTU to be sent a copy. This will be used to perform in-house monitoring of the consent process. Copies of ICFs will contain identifiable personal data which will be stored at the BCTU separately from the trial record and other participant data.

The Investigator must maintain documents not for submission to BCTU (e.g. **Participant Recruitment and Identification Logs**) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

BCTU, CHaRT and TextLocal will maintain the confidentiality of all participant's data and will not disclose information by which participants may be identified to any third party other than those directly involved in the treatment of the participant and organisations for which the participant has given explicit consent for data transfer (e.g. Sponsor) or explicit consent to be contacted. Representatives of the iHOLDS Trial Office and Sponsor may be required to have access to participant's notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times.

19. FINANCIAL AND OTHER COMPETING INTERESTS

There are no financial or other competing interests associated with this trial protocol.

20. INSURANCE AND INDEMNITY

This is a Clinician-initiated trial. The Sponsor (the 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, HS 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.

21. AMENDMENTS

The decision to amend the protocol and associated trial documentation will be initiated by the TMG. As Sponsor, Birmingham Women's and Children's NHS Foundation Trust will be responsible for deciding whether an amendment is substantial or non-substantial. Substantive changes will be submitted to REC, HRA and MHRA (where applicable) for approval. Once this has been received, Research and Development (R&D) departments will be notified of the amendment, and requested to provide their approval. If no response is received within 35 days, an assumption will be made that the site has no objection to the amendment and it will be implemented at the site as per the HRA national process. All amendments will be tracked in *Section 55 AMENDMENT HISTORY* in the protocol.

22. POST TRIAL CARE

All patients will continue to receive standard medical care following participation in the clinical trial. There are no interventions that participant's will be prevented from accessing after their participation in the trial has been completed.

23. PUBLICATION POLICY

As Sponsor, all data arising from the 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 iHOLDS trial, will be made available on the trial website (see *Section Administrative Information* for link).

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.

24. ACCESS TO FINAL DATA SET

Only the Trial Steering Committee will have access to the full trial dataset in order to ensure that the overall results are not disclosed by an individual trial site prior to the main publication. Following publication of the findings, the final trial dataset will be made available to external researchers upon approval from the Trial Management Group and the Sponsor.

25. AMENDMENT HISTORY

Non-Substantial Amendment 01 (NSA-01) dated 4th June 2021

Documents amended:

- Protocol version: 1.0a dated 13th May 2021
- PIL version 1.0a dated 12th May 2021
- ICF version 1.0b dated 12th May 2021
- Maternal Satisfaction Questionnaire v1.0 dated 12th May 2021

Protocol Section	*Summary of key changes*
N/A	Minor amendments and correction of minor mistakes found within the protocol
Reference Numbers	ISRCTN number added
Administrative Information	• TMG and Co-applicant Group list amended • Addition of iHOLDS Trial Office telephone number
4. Eligibility	• Definition of nulliparous women corrected • Propess and prostin eligibility criteria moved from inclusion to exclusion • Addition of new exclusion criteria: BMI of >40 at booking
7.5 Treatment Supply and Storage	Removal of submission of Pharmacy department daily fridge temperature readings to the Trial Office
11.4 Serious Adverse Events Reporting	• Removal of maternal pulmonary embolism as a maternal outcome • References added regarding relevantly qualified clinical co-applicant review of SAE causality and expectedness
12.2 Case Report Form Completion	Timelines for CRF return to the Trial Office added

Non-Substantial Amendment 02 (NSA-02) dated 12th October 2021

Documents amended:

- Protocol version 1.0b dated 7th October 2021

Protocol Section	*Summary of key changes*
N/A	Minor amendments and correction of minor mistakes found within the protocol
Administrative Information	• TMG and Trial Office contact details updated • DMC Statistician replaced
Trial Schema	Trial Schema replaced
3.3 Identification of Participants 5 Consent	Consent process clarified
7.1 Trial Treatment / Intervention	• Treatment regimen table updated to include infusion rate for 50 ml and 500 ml dilution • Instruction added to remove 2 ml of diluent if required prior to adding oxytocin • Current SPC version date amended
13.1 Site Set-up and Initiation	Details regarding clinical staff training added
15.2.3 Subgroup Analyses	Reference to “maternal ruptured membranes” subgroup analysis removed

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