UNIVERSITY OF BIRMINGHAM

BCTU Birmingham Clinical Trials Unit

IMP MANUAL

High or **L**ow **D**ose **S**yntocinon for **i**nduction of labour in nulliparous women: a double blind, randomised controlled trial

Version Number:	1.0
Version Date:	13-Dec-2021

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

Administrative Information

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

Trial Organisation	
Sponsor	Birmingham Women's and Children's NHS Foundation Trust
National Coordinating Centre	Birmingham Clinical Trials Unit (BCTU), University of Birmingham
Chief Investigator	Professor Sara Kenyon

Trial Office Contact Details	
Senior Trial Manager	Dee Wherton
Trial Manager	Smita Odedra
Lead Midwife	Kate Siddall
Senior Data Manager	Jack Toland
Postal address	BCTU, Public Health Building, Institute of Applied Health Research, University of Birmingham, Edgbaston, Birmingham, B15 2TT
Email address	iHOLDS@trials.bham.ac.uk
Telephone number	Trial Office: 0121 415 8298, Lead Midwife: 07816 363 582
Trial website	www.birmingham.ac.uk/iHOLDS
Trial social media	Twitter: @iHOLDSTrial

Third Parties	
IMP labelling and shipment	Sharp Clinical Services UK
Randomisation	The Centre for Healthcare Randomised Trials (CHaRT), University of Aberdeen

Web-based System (for entry of temperature data)

Website address	www.trials.bham.ac.uk/iHOLDSstudy

Amendments

The following amendments and/or administrative changes have been made to this IMP Manual since the implementation of the first version:

Date of amendment	Version number	Summary of amendment

Abbreviations

Abbreviation	Term
BCTU	Birmingham Clinical Trials Unit
IMP	Investigational Medicinal Product
ISF	Investigator Site File
PSF	Pharmacy Site File
SPC	Summary of Product Characteristics
SSDL	Site Signature and Delegation Log
TMG	Trial Management Group

Glossary of Documents

Document	Description	Schedule for Completion
(Labour Ward) Drug Accountability Log	Records receipt, dispensing, quarantine, local destruction and return of IMP to Pharmacy	Copy to be returned to BCTU following completion of each page or at request of BCTU. Copy to be retained in Investigator Site File and original returned to Pharmacy for filing
(Pharmacy) Drug Accountability Log	Records receipt, transfer to Labour Ward, return, quarantine and destruction of IMP	Copy to be returned to BCTU following completion of each page, following destruction of IMP or at request of BCTU. Original filed in Pharmacy Site File
Local Pharmacy Delegation Log	Delegation of trial related duties within the local Pharmacy by the designated Responsible Pharmacist	To be completed at site setup and maintained locally (not to be returned to the BCTU). Copy filed in Pharmacy Site File (or Note to File stating location)
Repeat Treatment Form	Midwife to complete if resupply of treatment is required for an existing trial participant	If required, details should be telephoned through to the Randomisation Line. Original form to be posted to BCTU and copy retained in participant's file
Site Signature and Delegation Log (SSDL)	To be signed by the Responsible Pharmacist, Principal Investigator and Research Midwife as a minimum to record delegation of trial related duties	To be completed at site setup and a copy provided to the BCTU. Updates to be made locally as required and further copies to be provided to the BCTU. Original to be filed in Investigator Site File
(Labour Ward) Temperature Deviation Form	Records and reports major IMP temperature deviations occurring in the Labour Ward	Following reporting of a major temperature deviation to the Randomisation Line, Pharmacy to be notified immediately. Pharmacy to complete form and return promptly to the BCTU. Original filed in Pharmacy Site File
(Pharmacy) Temperature Deviation Form	Records and reports minor and major IMP temperature deviations occurring in Pharmacy	To be completed and copy to be returned immediately to the BCTU following detection of a minor or major temperature deviation. Original filed in Pharmacy Site File
Temperature Monitoring Log (Labour Ward only)	Records temperature readings taken from calibrated temperature monitor (supplied by BCTU), of IMP stored in the Labour Ward fridge (Pharmacy will use own monitor and records)	To be completed on paper and entered monthly on the trial database (before the 5th of the next month). Failure to return may result in temporary recruitment suspension. Original to be returned to Pharmacy for filing

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1. Scope

This guidance has been developed to ensure sites are compliant with the UK clinical trials regulations and the advice contained within the Summary of Product Characteristics for oxytocin and the iHOLDS Trial Protocol.

2. Pharmacy Responsibilities

SUMMARY

- **Receiving drug**
- **Transferring drug to Labour Ward**
- **Pharmacy temperature monitoring**
- **Overseeing Labour Ward temperature monitoring**
- **Handling temperature deviations**
- **Destroying IMP as required**
- **Maintaining Pharmacy Site File**

- Pharmacy is responsible for ensuring that the iHOLDS Investigational Medicinal Product (IMP) is handled correctly following receipt in accordance with this document, the iHOLDS Protocol and current Summary of Product Characteristics.
- Ensure IMP is labelled in accordance with the guidelines in this document (see *Section 6. IMP labelling*).
- Temperature deviations must be reported and acted upon as detailed in this document (see *Section 9. Temperature deviations*).
- Damaged and/or expired IMP should be destroyed in accordance with this document (see *Section 8. IMP Return and Destruction*).
- The responsible Pharmacist for IMP oversight must sign the **Site Signature and Delegation Logs** (SSDL) filed within the Investigator Site File (ISF).
- The SSDL must be updated in the event of changes of responsibility of the responsible Pharmacist.
- The responsible Pharmacist will ensure that **Local Pharmacy Delegation Log** is maintained and filed in the Pharmacy Site File (PSF), or a Note to File stating its location if filed separately.
- The BCTU will provide a **Pharmacy Site File** (PSF) containing copies of all essential documentation, Summary of Product Characteristics (SPC), Drug Accountability Logs, temperature monitoring records and any subsequent amended documentation. The PSF must be maintained throughout the course of the trial. New versions of documents should be filed, and superseded versions of documents should be kept in the file and marked as superseded.

3. Trial IMP Description

IMP must only be used for the designated iHOLDS trial participant at randomisation. The investigational medicinal product (IMPs) are:

- Oxytocin 5 IU/ml Concentrate for solution for infusion
- Oxytocin 10 IU/ml Concentrate for solution for infusion

The treatment packaging is blinded. The cartons (size 12 cm x 7.7cm x 2cm) are **blue for iHOLDS** and contain two ampoules of oxytocin, either 2 x 5 IU or 2 x 10 IU units.

4. IMP COSTS

IMP will be provided free of charge by the Sponsor.

5. IMP SUPPLY AND ORDERING

The iHOLDS treatment packs are produced by Sharp Clinical Services, who supply the IMP directly to Pharmacy at site. Sites will not be required to order the IMP as the iHOLDS Trial Office will monitor IMP levels via the web-based system and will contact the site to arrange delivery when necessary.

The iHOLDS IMP will be shipped in temperature controlled vehicles and a temperature monitoring device (Temptale) will be supplied within the boxes by Sharp.

5.1 On receipt of IMP

5.1.1 On arrival at Pharmacy

- The instructions supplied with the Temptale Monitor should be followed (summarised below):
    - The device should be stopped from recording further temperature data
    - The relevant fields should be collected on the instruction sheet
    - The monitor should be attached to a PC via USB to generate a report
    - The report should be emailed to the iHOLDS Trial Office
- Contents of the shipment should be checked:
    - For signs of damage
    - To ensure they are correct and correspond with the enclosed shipment documents
- IMP should be moved promptly to fridges in Pharmacy for storage between 2-8^{o}C as per the SPC (in the event of a temperature excursion during shipment, see *Section 5.1.2* below)
- The **Pharmacy Drug Accountability Log** and web-based system should be updated to confirm receipt of the IMP
- A valid certificate of analysis and copies of the QP certificates sent with the shipment should be checked to ensure they correspond with the batch delivered, and filed in the Pharmacy Site File.

5.1.2 In the event of a temperature excursion during shipment

- The Temptale Monitor will alarm
- IMP should be quarantined within the fridge between 2-8^{o}C (until determined as fit for use by the iHOLDS Trial Office following review of the report)
- Complete the Temperature Deviation Form and send to the iHOLDS Trial Office with a copy of the Temptale data
- Await a decision from the iHOLDS Trial Office as to whether IMP is fit for use or should be destroyed.

6. IMP LABELLING

Sharp Clinical Services will provide participating hospital sites with packaged and labelled IMP.

Trial specific Annex 13 compliant labels are applied to the carton and ampoules by Sharp. Due to the blinded nature of the trial, the carton label states that the treatment pack contains either 2 x 5 IU ampoules *or* 2 x 10 IU ampoules. On receipt of an appropriate prescription, the Participant Number, Principal Investigator and Site Name or Number should be written on the label by the Midwife as per local practice.

A syringe/bag label is also provided to ensure the infusion is labelled correctly. The relevant participant identifiers should be added to the label by the Midwife, in addition to the details of IMP preparation and checking as requested on the label.

See below for example IMP labels (copies are also filed within the Pharmacy Site File and Investigator Site File (ISF):

Figure 1: Example carton label

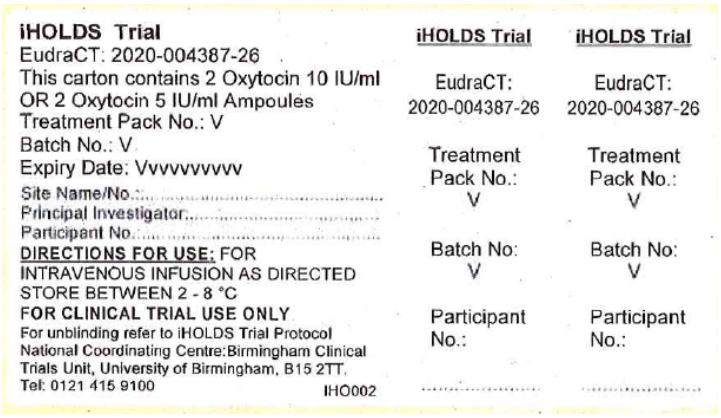


Figure 2: Example ampoule label

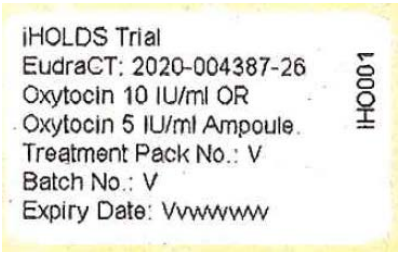
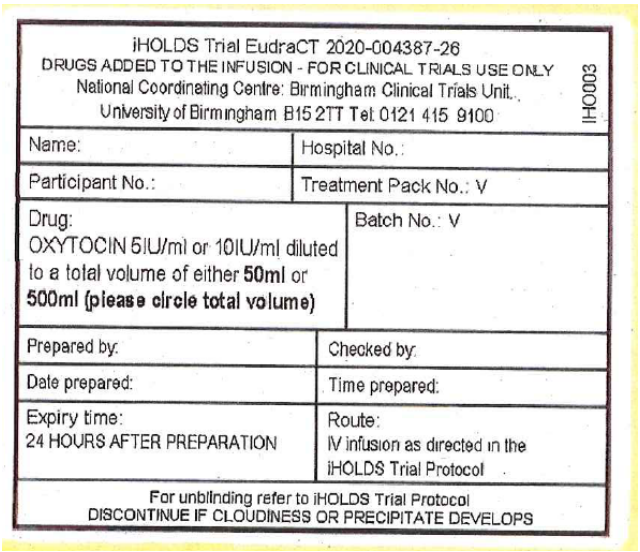


Figure 3: Example infusion bag/syringe label



7. IMP Storage and Monitoring

iHOLDS IMP must be stored between 2-8°C as stated in the SPC, however if the IMP temperature reaches up to 30°C it can be returned to the fridge and used for a maximum of three months, after which time it must be discarded.

The responsible Pharmacist at site is responsible for the storage of the IMP in Pharmacy and must have oversight of IMP stored on the Labour Ward. The BCTU Trials Office will notify Pharmacy and the Research Midwife when Labour Ward stock is running low and should be replenished. The Research Midwife is responsible for collecting IMP from Pharmacy to ensure adequate supplies, and restocking the Labour Ward. Provisions should be made when the Research Midwife is absent.

7.1 Allocation of IMP to Labour Ward

The IMP will be stored in Pharmacy upon delivery to site. In order to allocate IMP to the Labour Ward (or Delivery Suite):

- Pharmacy will access the web-based system and state how many treatment packs are required for transfer to the Labour Ward (following agreement with the Research Midwife).
- The web-based system will then reveal the treatment pack numbers to transfer. Email notification will automatically be sent to Pharmacy with details of these packs.
- In order to ensure the correct treatment pack numbers are selected from Pharmacy, this notification must be printed out and manually checked against treatment packs selected.
- Pharmacy must then access the web-based system to confirm that the IMP has been allocated to the Labour Ward; the treatment packs will not be available for randomisation until this step is completed.
- The paper **Pharmacy Drug Accountability Log** should be updated to reflect the transfer of stock. Email printouts of treatment pack numbers for transfer should be filed with the Pharmacy Drug Accountability Log in the Pharmacy Site File (PSF).
- The IMP must be transferred under temperature controlled conditions within a provided cool bag.
- If IMP is likely to be out of the fridge for more than 10 minutes, it should be transferred with a calibrated temperature monitor. In this case, the temperature on departure from Pharmacy and arrival at the Labour Ward must be documented on the **Temperature Monitoring Log** (see *Section 7.3 Temperature Monitoring Log*).
- The IMP must be placed in the designated area in the Labour Ward fridge promptly after arrival.
- The local Research Midwife or delegated member of staff must complete the paper **Labour Ward Drug Accountability Log** to reflect the receipt of treatment packs from Pharmacy.

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.

7.2 IMP storage

iHOLDS IMP must be stored between 2-8°C and must be segregated from other stock in the fridge. If stored in the same fridge, HOLDS and iHOLDS stock should be stored on separate shelves. The designated storage area must be labelled "iHOLDS Trial stock for clinical trial use only". Storage must allow for airflow around the IMP within the fridge.

The calibrated temperature monitor on the Labour Ward will be set up to alarm in the event of a major deviation (<2˚C and ≥30˚C) whereby the site must call the randomisation line to temporarily suspend recruitment at the site*. Pharmacy may use their own calibrated temperature monitoring device.

*See *Section 9. Temperature deviations* of IMP Manual for more details regarding temperature deviations.

7.3 Temperature Monitoring Log

7.3.1 Labour Ward: Daily temperature recording and reporting

Labour Ward fridge temperatures must be continuously monitored and daily readings of the maximum and minimum must be recorded on the paper HOLDS/iHOLDS **Temperature Monitoring Log**. Arrangements must be made at site to ensure readings are recorded daily, which should include weekends/bank holidays etc.

Daily maximum and minimum readings must be taken using a calibrated temperature monitor supplied by the iHOLDS Trial Office. The buffered probe must be placed next to the IMP within the fridge and the maximum and minimum temperature readings recorded. Set up instructions for the calibrated temperature monitor will be supplied to Pharmacy who will be responsible for setting up the temperature monitor on the Labour Ward.

Daily temperature readings must firstly be recorded on the paper Temperature Monitoring Log before submitting via the web-based system at least once per month. The original paper copy should be returned to Pharmacy for filing in the Pharmacy Site File.

If HOLDS trial stock is stored in the same fridge as iHOLDS stock, daily temperature readings for both studies may be recorded on the same Temperature Monitoring Log using the same device, however data should still be recorded in both trial databases (see *Section 7.4 Record keeping* for more details).

Temperature Monitoring Logs must be entered into the database by the 5th of the month for the previous month (e.g., figures for January must be submitted by the 5th February at the latest). Failure to return this information could result in the temporary suspension of recruitment at a site.

Following entry of the daily temperature recordings at site, the automated pack management system will ensure that expiry dates of treatment packs are reduced to 3 months for recorded minor temperature deviations (>8 ˚C and <30 °C) in line with the SPC.

Sites own paper temperature monitoring logs can be used providing the same information is captured and it has been approved by the iHOLDS Trial Office before use.

7.3.2 Temperature recording of IMP out of the fridge >10 minutes

When IMP is moved from Pharmacy to the Labour Ward it is important that it is moved in temperature controlled conditions (see *Section 7.1 Allocation of IMP to Labour Ward*). If the IMP is likely to be out of the fridge for longer than 10 minutes, the temperature should be monitored using a temperature monitoring device during transport and logged on the **Temperature Monitoring Log.** The temperature should be recorded before leaving Pharmacy and on arrival at the Labour Ward (immediately before putting in the fridge). If IMP is removed from the fridge for any other reason for >10 minutes, these details should also be documented. Both situations should be recorded on the second table of the Temperature Monitoring Log.

7.4 Record keeping

Paper **Temperature Monitoring Logs** form part of the trial records (source data). Following entry into the database, the original should be returned to the Pharmacist for filing in the Pharmacy Site File. These records must be made available for monitoring visits and stored in a secure limited access storage area. All personnel involved with dispensing and temperature monitoring of iHOLDS IMP should be aware of their location.

Where the same paper Temperature Monitoring Log is being used for iHOLDS and HOLDS, the original should be filed in one PSF with a photocopy filed in the other study PSF. The PSF containing photocopies should have a Note to File stating the location of the originals.

8. IMP Return and Destruction

No IMP will be returned from the participant as the dose is administered intravenously by site staff to the participants whilst in hospital.

IMP may need to be destroyed if it is damaged, expired or spoiled e.g. due to a temperature deviation (see *Section 9. Temperature deviations* for more details regarding temperature deviations).

8.1 Damaged IMP

- IMP destruction should be performed or arranged by Pharmacy. However if an ampoule is damaged on the Labour Ward, it may be necessary to dispose of it safely on the Labour Ward.
- In this instance, the treatment pack carton must be given to Pharmacy for accountability purposes and the **Labour Ward Drug Accountability Log** should be updated accordingly.
- Once the treatment pack records on the **web-based system** and the **Pharmacy Drug Accountability Log** in the Pharmacy Site File have been updated, the IMP (or carton if IMP destroyed on Labour Ward) can be destroyed.
- Pharmacy should:
    - Complete local disposal/destruction paperwork (in accordance with local policy [where applicable])
    - Provide evidence of disposal/destruction (where available) to the iHOLDS Trial Office when available (paperwork/certificate confirming process), together with an updated copy of the **Pharmacy Drug Accountability Log** reflecting destruction of the IMP/carton.
- If damaged IMP is taken from the Labour Ward fridge, Pharmacy will also need to allocate replacement IMP from Pharmacy via the web-based system to re-stock the Labour Ward fridge promptly (see *Section 7.1 Allocation of IMP to Labour Ward* of the IMP Manual).
- Re-ordering of IMP will be actioned by the BCTU following notification via the web-based system that IMP has been removed from the system.

8.2 Expiring IMP – Pharmacy and Labour Ward

- When the IMP is due to expire, an automated email will be sent to Pharmacy 10 days and 5 days before the IMP is automatically removed from the system.
- The email will contain the IMP pack number(s) to be destroyed. The email should be received before IMP is removed from the fridge.
- The expired IMP will then need to be quarantined and destroyed in accordance with local practice.
- If expired IMP is taken from the Labour Ward fridge, the **Labour Ward Drug Accountability Log** should be updated accordingly. Pharmacy will also need to allocate replacement IMP from Pharmacy via the web-based system to re-stock the Labour Ward fridge promptly (see *Section 7.1 Allocation of IMP to Labour Ward* of the IMP Manual).
- Pharmacy should:
    - Seek authorisation from the iHOLDS Trial Office to destroy the expired stock
    - Complete local disposal/destruction paperwork (in accordance with local policy [where applicable])
    - Provide evidence of disposal/destruction (where available) to the iHOLDS Trial Office when available (paperwork/certificate confirming process), together with a copy of the updated **Pharmacy Drug Accountability Log** reflecting destruction of the IMP.
- Re-ordering of IMP will be actioned by the BCTU following notification via the web-based system that IMP has been removed from the system.

9. TEMPERATURE DEVIATIONS

For the purpose of the iHOLDS trial, a temperature deviation is defined as any period of time that the temperature of the IMP has fallen below 2˚C or risen above 8˚C. iHOLDS IMP must be stored between 2-8°C as stated in the SPC, however if the IMP temperature is recorded between 8-30°C, it can be stored and used for a maximum of three months, after which time it must be discarded.

- *Major temperature deviations:* If a deviation below 2˚C or 30˚C and above occurs on the Labour Ward, staff will be alerted by the alarm on the calibrated temperature monitor which requires immediate action by reporting via the Randomisation Line and completing a **Temperature Deviation Form** (see *Section 9.1* below). Major deviations will be investigated by the iHOLDS Trial Management Group (TMG) which may trigger a monitoring visit.
- *Minor temperature deviations:* Deviations more than 8˚C and less than 30˚C will be reported via the **Temperature Monitoring Log** (see *Section 9.2* below).

9.1 Actions to be taken: Major Temperature Deviations (<2°C or ≥30°C)

In the event of the IMP temperature falling below 2 °C or rising to 30 °C or above for any period of time, all affected IMP must be immediately quarantined **and must not be given to participants**. The responsible Pharmacist (as recorded on the Site Signature and Delegation Log) is responsible for ensuring that the appropriate actions are taken.

9.1.1 Major temperature deviations (<2°C or ≥30°C) occurring on the Labour Ward

- The 24-hour automated randomisation telephone line (0800 280 2307) must be called **immediately** and option 3 "report a major temperature deviation" should be selected. **This will automatically suspend recruitment at site**.
  Note: Where HOLDS and iHOLDS stock are stored in the same fridge, this process *must* be repeated for both studies.
- The iHOLDS Trial Office and the local site team (including Pharmacy) will automatically be alerted via email that a temperature deviation requiring IMP quarantine and recruitment suspension has occurred at site.

- The IMP must be immediately placed into quarantine by staff on the Labour Ward:
    - The affected treatment packs should be placed in a quarantine bag sealed with a signed and dated label. (The iHOLDS Trial Office will supply quarantine bags and labels, two sets will be stored with the treatment packs in the Fridge and further packs will be stored in the Pharmacy and Investigator Site File).
    - The **Labour Ward Drug Accountability Log** should be updated to confirm which treatment packs have been quarantined.
    - The quarantined IMP should be temporarily stored in a lockable drug cupboard on the Labour Ward with access restricted to trained study personnel only. Quarantined IMP may be returned to the fridge if insufficient storage available in the drug cupboard. The location should be documented on the Log.
    - Quarantined IMP should be returned to Pharmacy as soon as possible. The **Labour Ward Drug Accountability Log** should be updated to reflect the stock has moved to Pharmacy.
- The Pharmacist should complete and report a **Labour Ward Temperature Deviation Form** to the iHOLDS Trial Office as soon as possible.
- Pharmacy will investigate any deviation and restock the Labour Ward IMP from the Pharmacy stock as soon as possible, ideally within 48 hours to ensure recruitment can resume as soon as possible.
- On receipt of quarantined stock, Pharmacy should:
    - Seek authorisation from the iHOLDS Trial Office to destroy the stock.
    - Follow local quarantine and subsequent destruction procedures (in accordance with local policy [where applicable]).
    - Complete local disposal/destruction paperwork and provide evidence of disposal/destruction to the iHOLDS Trial Office by email when available, together with a completed copy of the relevant **Pharmacy Drug Accountability Log** confirming destruction.
- Following TMG review of the Temperature Deviation Form, further investigation (which may include a monitoring visit) may be indicated.

9.1.2 Major temperature deviations (<2°C or ≥30°C) occurring in Pharmacy

- The IMP must be immediately placed into quarantine by following local Pharmacy quarantine procedures.
- A **Pharmacy Temperature Deviation Form** must be completed and returned to the iHOLDS Trial Office as soon as possible by email.
- The Pharmacist must seek approval from the iHOLDS Trial Office to destroy the stock.
- Disposal/destruction paperwork will be completed by Pharmacy and notification of disposal/destruction will be provided to the iHOLDS Trial Office by email when available, together with a completed copy of the **Pharmacy Drug Accountability Log** confirming destruction.
- Following TMG review of the Temperature Deviation Form, further investigation (which may include a monitoring visit) may be indicated.

9.2 Actions to be taken: Minor Temperature Deviations (>8 °C - <30°C)

In the event of the IMP temperature going above 8°C but below 30°C the SPC states that the IMP "can be stored up to 30°C for three months, but then must be discarded" therefore the IMP **does not need** to be quarantined.

9.2.1 Minor temperature deviations (>8°C - <30 °C) occurring on the Labour Ward

- Labour Ward staff should notify Pharmacy of the fridge temperature going out of range (as per local practice). No further immediate actions are required by the Labour Ward staff, and recruitment does not need to be suspended.
- Following monthly entry of the **Temperature Monitoring Log** into the web-based system (see *Section 7.3 Temperature Monitoring Log*) the expiry dates for affected product will be reduced in the randomisation system and affected IMP will be allocated first.
- The local Pharmacy will be sent notification of the treatment packs affected and the new expiry date by the web-based system for information.
- Stock at site will not be re-labelled with the reduced expiry date and will be automatically removed from the randomisation system after three months and the Pharmacist will be instructed to remove the IMP from the fridge. See *Section 8. IMP Return and Destruction* for further detail on removal and destruction of IMP.

9.2.2 Minor temperature deviations (>8°C - <30 °C) occurring in Pharmacy

- The iHOLDS Trial Office must be notified as soon as possible by completing and returning a **Pharmacy Temperature Deviation Form** by email.
- IMP expiry dates will be automatically updated in the system and affected IMP will be allocated first. It is good practice for Pharmacists to segregate expiring stock from other stock (the expiry date on the web-based system should be used as opposed to the carton expiry date which may have since changed).
- Pharmacy will be sent confirmation of the treatment packs affected and the new expiry date for information.
- Stock at site will not be re-labelled with the reduced expiry date and will be automatically removed from the system after three months. See *Section 8. IMP Return and Destruction* for further detail on removal and destruction of IMP.

10. IMP Preparation and Administration

Maternity Units must fully comply with the regimens of oxytocin described for the trials. If the regimen you currently use differs in any way we recommend that you consider using an identified system (IVAC or Pump – ideally pre-programmed with the trial infusion rate).

Oxytocin should be administered as an intravenous (IV) drip infusion or, preferably, by means of a variable-speed infusion pump. Mix the bag by gently inverting to ensure homogeneity of the dose.

Please see **Table 1** and **Table 2** below for 50ml and 500ml regimes. Two ampoules of either 5iu (2 x 5iu/1ml ampoules – 10iu/2ml in total) or 10iu (2 x 10iu/1ml ampoules – 20iu/2ml in total) need to be added to the diluent (sodium chloride 0.9% or appropriate alternative) which should be made up to a total of either 50ml or 500mls:

10.1 50ml Syringe Pump

Each ampoule contains 1ml of oxytocin:

1. Ensure the x2 ampoules of oxytocin (2mls) are added to **48mls** of diluent (sodium chloride 0.9% or appropriate alternative)
2. This may require 2mls of diluent to be withdrawn from 50mls **BEFORE** adding the x2 ampoules of oxytocin
3. **The total volume of oxytocin plus diluent should always be 50mls**
4. Ensure the x2 ampoules of oxytocin are added to the diluent **BEFORE** inserting & priming the tubing

Table 1: 50ml syringe pump - oxytocin regimen

Time after starting (mins)	Volume infused (mls/hour)
	Dilute x2 ampoules oxytocin with the diluent (0.9% Sodium Chloride or alternative)
0	0.6
30	1.2
60	2.4
90	3.6
120	4.8
150	6.0
180	7.2
210	8.4
240	9.6

10.2 500ml Infusion pump

Each ampoule contains 1ml of oxytocin:

1. **WITHDRAW 2mls of the diluent** (0.9% sodium chloride or appropriate alternative) **BEFORE** adding the x2 ampoules of oxytocin (2mls)
2. **The total volume of oxytocin plus diluent should always be 500mls**
3. Ensure the x2 ampoules of oxytocin are added to the diluent **BEFORE** inserting & priming the tubing

Table 2: 500ml infusion pump - oxytocin regimen

Time after starting (mins)	Volume infused (mls/hour)
	Dilute x2 ampoules oxytocin with the diluent (0.9% Sodium Chloride or alternative)
0	6
30	12
60	24
90	36
120	48
150	60
180	72
210	84
240	96

11. Participant Randomisation and Treatment Resupply

11.1 Randomisation process

Randomisation will occur when eligibility has been confirmed by an iHOLDS trained Obstetrician and informed consent has been obtained. The randomisation process is completed via telephone to the Randomisation Line at the Centre for Healthcare Randomised Trials (CHaRT), University of Aberdeen (0800 280 2307). Each trial will have a unique 6-digit trial ID code to enter. Randomisation will be available 24 hours a day.

Notification of participant randomisation will be sent immediately following randomisation to the BCTU and site staff, including Pharmacy, via email; this is sent to Pharmacy for information purposes only. The email must be printed out and filed in the Pharmacy Site File and Investigator Site File.

The email notification will confirm the following participant's details:

- Date of birth
- Date and time of randomisation
- Participant Number
- Treatment Pack Number

11.2 Resupply of treatment

Resupply of subsequent treatments, should they be required, will be requested via the same secure system to guarantee allocation to the same dose as initial randomisation. The Midwife should therefore complete an iHOLDS **Repeat Treatment Form** and contact the Randomisation Line, selecting the relevant option for repeat treatment.

All trial participants will be randomised one treatment pack and an additional spare will be reserved should a second allocation be required. One high dose and one standard dose treatment pack will also be reserved for use by any participant requiring a third allocation.

11.3 Randomisation methodology

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
- Prostaglandin for cervical ripening or not
- 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.

12. UNBLINDING

Unblinding of participants as an emergency will not be required as the management of these women will not change in the light of dose 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 BCTU 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.

13. PHARMACY MONITORING

Monitoring visits will be performed by the Sponsor, Birmingham Women's & Children's NHS Foundation Trust, in accordance with the iHOLDS Monitoring Plan. The responsible Pharmacist should make every effort to be available to meet with the Monitor during site visits.

A Monitoring Report giving details of checks performed and issues noted by the Monitor during an on-site monitoring visit will be sent to site following a visit. Actions specified in the report must be completed, the Monitor must be notified of completed actions, and the Monitoring Report must be filed in the PSF. Follow up letters from monitoring visits must be placed in the PSF.

14. PHARMACY ARCHIVING

The Pharmacy Site File for the iHOLDS Trial must be archived along with all the essential trial documentation and source records (e.g. signed Consent Forms, Case Report Forms etc.) at site, and must be securely retained for at least 25 years after the end of the trial. Please note, these dates will differ for each study. Participating sites will be sent a letter specifying the permissible disposal date.

15. PHARMACY FILING

General correspondence/reports must also be filed in the relevant section of the PSF.