High Or Low Dose Syntocinon® for delay in labour: the HOLDS trial

Protocol

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Signatures

The Principal investigators and the sponsor have discussed this protocol. The Principal investigators agree to perform the investigation and to abide by this protocol except in case of medical emergency or where departures from it are mutually agreed in writing.

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1 Trial summary

Title

High Or Low Dose Syntocinon® for delay in labour (HOLDS)

Settings

Obstetric departments in approximately 30 hospitals within the UK.

Trial Design

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

Aims

Primary objective:

- To perform a robust multicentre, randomised, double blind controlled trial to evaluate the effect on CS rate of high dose regimen versus standard dose regimen oxytocin for nulliparous women at term (37-42 weeks gestation) with confirmed delay in the first stage of labour using NICE definitions.

Secondary objectives are to:

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

Target Population

Nulliparous women with a singleton cephalic pregnancy at term (37-42 weeks gestation) with confirmed delay in labour and ruptured membranes as defined by NICE Intrapartum Care Guideline [NICE 2014] for whom the clinical decision has been made to prescribe Syntocinon for augmentation of labour.

Health Technologies Assessed

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

2 Lay Summary

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

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

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

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

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

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

3 Contacts and Roles

3.1 Sponsor and Sponsor Roles

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

3.2 Trials Office

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4 Abbreviations

AE	Adverse event
AR	Adverse reaction
ASR	Annual Safety Report
BCTU	Birmingham Clinical Trials Unit at the University of Birmingham
BWNFT	Birmingham Women's NHS Foundation Trust
CI	Chief Investigator
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
ISRCTN	International Standard Randomised Controlled Trial Number
MREC	Multicentre Research Ethics Committee
PDF	Portable Document Format
PI	Principal Investigator – the local lead investigator
PIS	Participant Information Sheet
RR	Relative Risk
RSI	Reference Safety Information
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

5 Background

HOLDS Is a multicentre, randomised, double-blind randomised controlled trial to evaluate whether a high dose regimen oxytocin for nulliparous women delayed in the first stage of labour reduces the Caesarean section (CS) rate. These women have a relatively high rate of unplanned CS[1] (34%) and making sure the rate is as low as possible is important as unplanned CS is associated with longer stay in hospital, higher risk of infection, bleeding and blood clots and is associated with an increased risk of CS in subsequent pregnancies[2,3,4].

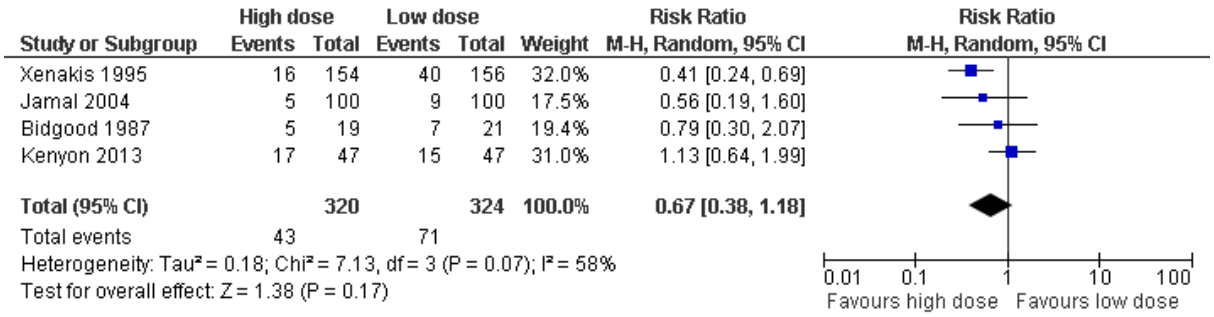
Robust evidence as to how best to care for women with delayed labour is lacking and it is a research priority for the Royal College of Obstetricians and Gynaecologists (RCOG). The length of labour for nulliparous women is on average 8 hours and it is unlikely to last over 18 hours[5]. In line with NICE guidance[5] once a woman is in established labour (i.e. she has regular painful contractions and her cervix is 4cms or more dilated on examination) assessment of progress includes cervical dilation as well as descent and rotation of the baby's head and changes in the strength, duration and frequency of uterine contractions. Should delay be suspected (when cervical dilation of <2cm in four hours is found) the woman remains under the care of a midwife, providing all other parameters remain normal. During the two hour period until progress is re-assessed the midwife is likely to suggest interventions which would facilitate progress occurring. The midwife caring for the woman would encourage the woman to mobilise, consider hydration (e.g. a sports drink), and discuss appropriate and effective pain relief. If her membranes are still intact, artificial rupture (amniotomy) will also be advised. Once delay is confirmed if cervical progress < 1cm found on re-assessment, transfer to obstetric-led care would take place (if required) for an obstetric review and a decision about management options. The only recommended treatment is Syntocinon® which is an inexpensive licensed synthetic version of the hormone oxytocin. It is routinely given by intravenous infusion to stimulate contractions leading to birth.

5.1 Evidence for the dose regimen of oxytocin

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

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

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



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

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

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

5.2 Additional relevant evidence

In the USA the Consortium of Safe Labor have recently published data that suggests that duration of labour appears longer today than in the past[10] and that a cervical dilation of 6 cm appears to be a better marker for the start of the active phase of labour. This has been adopted by the American College of Obstetricians and Gynecologists with the Society for Maternal-Fetal Medicine in their consensus statement for 'Safe Prevention of Primary Caesarean Section'[11] as part of a number of strategies designed to reduce the caesarean section rate. In this statement they suggest that intervention for delayed labour should not start until the cervix is more than 6cms dilated and it is not clear what the standard oxytocin dose regimen should be. Using the data collected as part of the work undertaken by the Consortium of Safe Labor, an observational study[12] found no difference in CS rates with a so-called high dose oxytocin compared to a low dose. However, this study is open to methodological biases, the exact oxytocin dose regimens are unclear and, as they are presented within the paper, all the regimens would be considered standard dose regimens in the UK. Uptake of this evidence and the Consensus Statement[11] has been controversial in the USA[13] and is unlikely to influence practice in the UK[14]. To ensure that the trial results will be of worldwide interest and relevance we will incorporate subgroup analysis of women commencing treatment less than 6cm and equal to or more than 6cm into our *a priori* statistical analysis plan.

6 Trial aim and objectives

6.1 Aim

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

6.2 Primary objective

- To perform a robust multicentre, randomised, double blind controlled trial to evaluate the effect on CS rate of high dose regimen versus standard dose regimen oxytocin for nulliparous women at term (37-42 weeks gestation) with confirmed delay in the first stage of labour using NICE definitions.

6.3 Secondary objectives

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

7 Trial design

7.1 Design

Multicentre, pragmatic, randomised, double blind controlled trial.

7.2 Setting

Delivery Suite of approximately 30 Maternity Units within the UK.

7.3 Inclusion criteria

- Nulliparous women with singleton cephalic pregnancy at term (37-42 weeks gestation)
- Confirmed delay in labour and ruptured membranes for whom the clinical decision has been made to prescribe Syntocinon for augmentation of labour

According to NICE guidance [NICE 2014], labour is established when there are regular painful contractions and progressive cervical dilation from 4 cm. Delay is suspected when cervical dilation of

< 2 cm in 4 hours occurs once labour is established. Delay is confirmed when progress of <1 cm in 2 hours is found on repeat vaginal examination.

7.4 Exclusion criteria

- Multiparous women
- Nulliparous women who:
  - have reached full dilation of the cervix (10cms)
  - are undergoing induction of labour
  - have a BMI >40 at booking
  - have a multiple pregnancy
  - have existing cardiac disease, bleeding disorders, diabetes (either pre-existing or gestational), previous uterine surgery
  - have had significant antepartum haemorrhage
  - are under 16 years of age
  - have a known contra-indication to oxytocin therapy as listed in the Summary of marketing Product Characteristics (SPC)

7.5 Identifying potential participants

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

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

7.6 Obtaining informed consent

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

In line with NICE guidance once a woman is in established labour (i.e. she has regular painful contractions and her cervix is 4cms or more dilated on examination) assessment of progress includes cervical dilation as well as descent and rotation of the baby's head and changes in the strength, duration and frequency of uterine contractions. Should delay be suspected (when cervical dilation of <2cm in four hours is found) the woman remains under the care of a midwife. During the two hour period until progress is re-assessed the midwife is likely to suggest interventions which would facilitate progress occurring. She would encourage the woman to mobilise, consider hydration (e.g. a sports drink), and discuss appropriate and effective pain relief. If her membranes are still intact,

artificial rupture (amniotomy) will also be advised. It is during this two hour window that the HOLDS trial would be discussed and so the midwives role in introducing the trial and answering any questions she may have is vital.

Once delay is confirmed transfer to obstetric-led care would take place (if required) for an obstetric review and a decision about management, including the use of oxytocin. Once more the midwives' role is fundamental in ascertaining if the woman is potentially eligible, explaining the trial, answering any questions she may have and in providing continuous support.

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

Confirming eligibility and obtaining consent to participate should be performed by someone with appropriate Good Clinical Practice (GCP) training and the oxytocin will be prescribed by an obstetrician. The midwives will receive appropriate and relevant training on the study protocol, and safety reporting mechanisms for the study to enable them to introduce the trial, answer any questions, randomise the woman and record dispensing of the trial Investigational Medicinal Product (IMP). She/he would then continue to manage the woman as care is not different between the two trial arms. The administration of IMP, and clinical care would normally be undertaken by such clinical midwives and therefore falls within their normal sphere of clinical practice. Therefore, the dispensing of the oxytocin can be recorded in the trial drug reconciliation chart by the midwife responsible for the woman's care and not necessarily by an obstetrician. The only difference is the strength of oxytocin and allocation is double blinded to participants, clinicians and the research team.

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

7.7 Informing the participants GP

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

7.8 Co-enrolment

Women participating in the HOLDS study cannot join other interventional trials of an IMP or procedure for delay in labour. They may be recruited to other intrapartum IMP studies. Women may be recruited to non-interventional trials such as observational or qualitative studies for delay in labour and to all other trials in pregnancy or the postnatal period.

8 Randomisation

Randomisation will be by telephone via an automated secure system developed by the Health Services Research Unit at Aberdeen University. Eligibility will be confirmed as part of the recruitment process and checked by the automated telephone randomisation system. Although some identifiable data is provided it is insufficient to constitute personal identifiable data.

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

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

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

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

8.1 Treatment allocation

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

Women randomised to the standard dose will receive a solution containing 2 x 5iu ampoules in 50mls (see Table 1) or 500mls (see Table 2) and those to the high dose a solution containing 2 x 10iu in 50 mls (see Table 1) or 500mls (see Table 2). Ampoules are manufactured as 5 and 10 iu and these regimens have been selected to enable the trial to be double-blinded. It is cheap (£2 per treatment) and licensed for this specific use in pregnancy- we intend to use it marginally outside the recommended maximum dose (shaded area). Synthetic oxytocin is manufactured by Novartis and called Syntocinon ®.

The standard dose regimen includes 2 ampoules of 5iu oxytocin and the high dose 2 ampoules of 10iu oxytocin with 50mls (or 500mls) of normal saline to ensure double blinding. Ampoules are only manufactured in 5 and 10iu and treatment packs contain 2 ampoules and will be stored in a fridge on Delivery Suite. Once made up the expiry time for the infusion is 24 hours.

The trial treatment packs may be stored in a separate fridge or in a designated compartment labelled for 'drugs to be used in HOLDS trial' depending on the conditions of the participating hospital's R&D approval. The fridge temperature should be maintain at 2-8C but no special monitoring arrangements are required. As the Summary of Product Characteristics indicates that Oxytocin can

be stored at 30°C for up to 3 months before being unusable, brief and small temperature excursions do not require quarantining of the IMP. Full instructions for IMP handling will be provided in a Pharmacy Manual.

A record will be kept of trial drugs dispensed. A trial-specific, structured dispensing log is provided to record the date and trial number against the treatment pack. An obstetrician will prescribe the IMP as 'Oxytocin for HOLDS study' on the participant prescription chart.

The attending obstetrician, clinical midwife or research midwife administering the randomised IMP will be required to record the initial dose and dose escalations on the Labour form.

8.2 IMP accountability and monitoring compliance

The local clinical trial pharmacist will be responsible for the storage and re-stocking the fridge on Delivery Suite. Pack usage will be monitored centrally by the Trial Office and stock sent from Sharps to the trial site. Pack use will be recorded by the recruiting site and monitored and reviewed by the trial office. Should packs be wasted for whatever reason they should be returned to pharmacy and removed from the computer system.

Table 1: Regimens proposed by HOLDS diluted in 50mls

		Dose of oxytocin (mU/min)	
Time after starting (mins)	Infusion rate (mls per hour)	Standard strength 10 iu in 50mls	High strength 20iu in 50mls
0	0.6	2	4
30	1.2	4	8
60	2.4	8	16
90	3.6	12	24
120	4.8	16	32
150	6.0	20	40
180	7.2	24	48
210	8.4	28	56
240	9.6	32	64

Table 2: Regimens proposed by HOLDS diluted in 500mls

		Dose of oxytocin (mU/min)	
Time after starting (mins)	Infusion rate (mls per hour)	Standard strength 10 iu in 500mls	High strength 20iu in 500mls
0	6	2	4
30	12	4	8
60	24	8	16
90	36	12	24
120	48	16	32
150	60	20	40
180	72	24	48
210	84	28	56
240	96	32	64

8.3 Care of women following randomisation until birth

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

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

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

- if the fetal heart rate (FHR) trace is normal, oxytocin may be continued until the woman is experiencing 4 or 5 contractions every 10 minutes. Oxytocin should be reduced if contractions occur more frequently than 5 contractions in 10 minutes,
- if the FHR trace is classified as non-reassuring , this should be reviewed by an obstetrician and the oxytocin dose should only continue to increase to achieve 4 or 5 contractions every 10 minutes,
- if the FHR trace is classified as abnormal, oxytocin should be stopped and a full assessment of the fetal condition undertaken by an obstetrician before oxytocin is recommenced.

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

should that be required for any reason, will depend on clinical circumstance and should follow normal clinical practice.

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

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

8.4 Breastfeeding

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

8.5 Summary of HOLDS data collection points and personnel

Process	Time	CRF	Person responsible
Confirm eligibility	When delay confirmed	Randomisation form	GCP and HOLDS trained obstetrician
Consent	Following confirmation of eligibility	Consent form	GCP and HOLDS trained obstetrician or midwife
Randomisation telephone call	Following confirmation of consent	Complete randomisation form	HOLDS trained obstetrician, midwife, student midwife or Maternity Support Worker
Prescription of drug	Following randomisation	Prescription chart	HOLDS trained obstetrician
Study treatment allocation	Following prescription of drug	Randomisation form and in medical notes	HOLDS trained midwife or obstetrician
Labour data collection	From commencement of study treatment until after birth	Labour form	HOLDS trained midwife
Birth outcome data collection	After discharge	Birth and discharge form	HOLDS midwife

8.6 Unblinding of trial participants

Unblinding of participants will not normally be necessary. Any adverse event that occurs from whichever trial treatment the woman is randomised to should be managed by the clinical team caring for the woman as per local protocols. The plasma half-life of oxytocin is approximately five

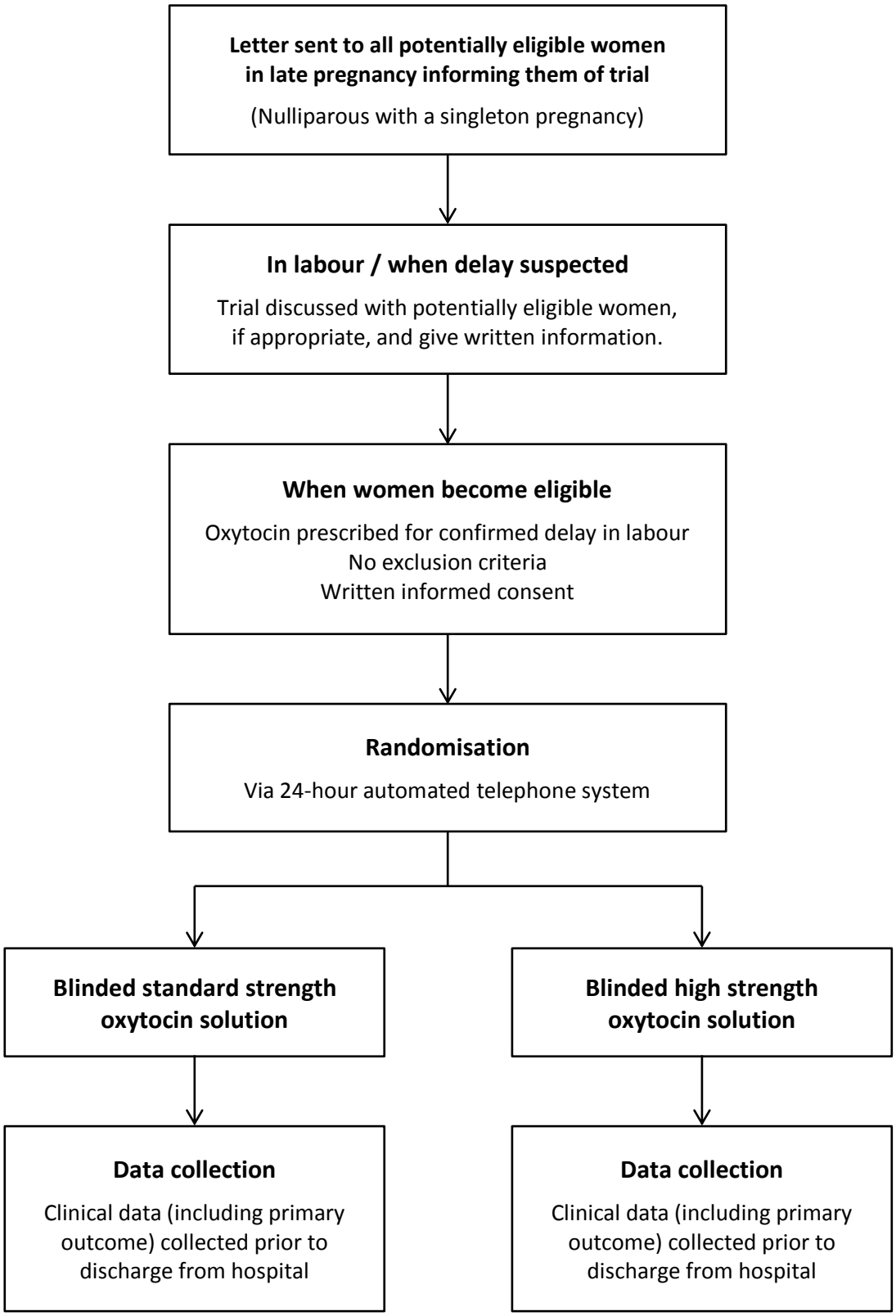
minutes, so should any cause for concern be identified, stopping the oxytocin is the most common and effective treatment rather than unblinding. However should this be required unblinding codes will be held in BCTU, with access through the local PIs and research midwives. Reasons for unblinding will be documented.

8.7 Withdrawal of trial/treatment or protocol violation

If a woman decides, after randomisation, she does not wish to be part of the trial, or there is a protocol violation, 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 or violations. The dose of oxytocin is titrated against uterine activity and the fetal heart rate, so it may be temporarily stopped and re-started as described in Section 8.3 above. Clear distinction will be made as to whether a participant is withdrawing from the trial but will still be followed up on an intention-to-treat basis, or whether the participant refuses any follow-up. If a participant explicitly withdraws consent to have any further data recorded their decision will be respected and recorded. All communication surrounding the withdrawal will be noted in the woman's hospital records and trial database, and no further data will be collected for that woman. If an SAE has occurred before her withdrawal we will follow this up to completion of the event.

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

8.8 Flow chart for HOLDS trial



9 Outcome measures

9.1 Primary Outcome

- Caesarean Section (CS)

9.2 Secondary maternal outcomes

Clinical outcomes

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

Process outcomes

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

9.3 Neonatal secondary outcomes include:

- Gender and birthweight
- Apgar score at 5 minutes

- Arterial cord blood gases when collected
- Breastfeeding rates on discharge from hospital
- Length of time after birth in hospital [days]
- Resuscitation
- Reason for neonatal review on ward (excluding routine baby check)
- Reason for admission to neonatal unit (NNU) and level of care received (level 1,2,3)including intensive care
- Duration of respiratory support
- Days to full oral feeds
- Seizures
- Neonatal encephalopathy (SARNAT grade)
- Therapeutic hypothermia (cooling) if required
- Intrapartum still birth
- Early neonatal death (within seven days of birth)

10 Safety Monitoring Procedures

The Medicines for Human Use (Clinical Trials) Regulations 2004 define categories of adverse events and it is the responsibility of investigators to notify safety events to the HOLDS Trial Office, who will forward these to the sponsor. It is the remit of the sponsor to report to the ethics committee and the MHRA. It is therefore imperative that all investigators have a thorough understanding of anticipated serious adverse events and the reporting process of these events.

10.1 General Definitions

10.1.1 Adverse Reactions (ARs)

An AR is an adverse event that is considered to have a “reasonable causal relationship” with any trial drug.

10.1.2 Adverse Events (AEs)

An AE is any unintentional, unfavourable clinical sign or symptom.

The following are <u>not</u> AEs and do <u>not</u> require reporting:

- A pre-existing condition (unless it worsens significantly during treatment).
- Diagnostic and therapeutic procedures, such as Caesarean section

10.1.3 Serious Adverse Reactions (SARs) or Serious Adverse Events (SAEs)

Any AR or AE that at any dose:

- Results in death
- Immediately threatens the life of participant*
- Results in hospitalisation or a longer than anticipated stay in hospital
- Results in a persistent or significant disability or incapacity

*Life-threatening in the definition of a serious adverse event refers to an event in which the mother was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. Important adverse events that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the pregnancy or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

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

10.1.4 Suspected unexpected serious adverse reactions (SUSARs)

A SUSAR is an SAE suspected to be related to a product, which is of a **type or severity** which is NOT consistent with the Summary of Product Characteristics (SPC) for oxytocin (see Section 10.2 for further details).

10.2 Expected Adverse Reactions (ARs)

Expected ARs are those listed in the current Summary of Product Characteristics (SPC) for oxytocin. These events do not meet the criteria of Suspected Unexpected Serious Adverse Reaction (SUSAR) unless for reason of their severity. For convenience, a summary of the expected ARs for oxytocin given in the SPC (as Syntocinon®, Novartis) are listed in Appendix One and Two (see SPC sections 4.8 Undesirable effects) and comprise the Reference Safety Information (RSI).

10.2.1 Expected ARs for maternal outcomes

There are a number of expected ARs in mother listed in section 4.8 of the SPC (see Appendix 1 & 2), which are considered to be of 'common' frequency and for convenience are listed, but are not limited to, below:

- headache
- nausea
- vomiting
- tachycardia/bradycardia

ARs occurring in mother will be recorded on the Labour Form. Occurrence will be confirmed by the local obstetrician and midwife, recorded on the CRF and returned to the Trial Office. They will be reported to the DMC when it meets.

10.2.2 Expected ARs for labour outcomes

There are a number of expected ARs for labour outcomes listed in section 4.8 of the SPC (see Appendix 1 & 2), which are considered to be of 'not know' frequency (i.e., isolated reports that cannot be estimated from the available data) and for convenience are listed, but are not limited to, below:

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

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

ARs occurring in labour will be recorded on the Labour Form. Occurrence will be confirmed by the local obstetrician and midwife, recorded on the CRF and returned to the Trial Office. They will be reported to the DMC when it meets.

10.3 Expected SARs

In addition to the definition of a SAR given in section 10.1.3, the following (listed for convenience, but are not limited) have a causal association with the trial drug and should be reported as a SAR:

- maternal anaphylaxis
- maternal pulmonary oedema

For details on how to report SARs please see Section 10.5 – Reporting of SARs/SAEs.

10.4 Expected SAEs

In addition to the definition of a SAE given in section 10.1.3, the following events (listed for convenience, but are not limited) do not have a causal association with the trial drug and should be reported as a SAE:

Maternal outcomes

- 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 as defined by national criteria categorised by us
- maternal death

Neonatal outcomes

- unexpected provision of neonatal **intensive** care
- neonatal seizures
- neonatal encephalopathy
- the need for neonatal therapeutic hypothermia and
- Intrapartum stillbirth
- neonatal death

For details on how to report SAEs please see Section 10.5 – Reporting of SARs/SAEs.

10.5 Reporting SARs/SAEs

All maternal or neonatal SARs/SAEs, from the commencement of the trial treatment until discharge from hospital, must be recorded on the SAE form and faxed to BCTU on 0121 415 9136 within 24 hours of the research staff becoming aware of the event. Alternatively, the report can be emailed as a PDF attachment to the HOLDS email address from a NHS email account. The Principal Investigator (or other nominated obstetrician) is required to assign seriousness, causality and expectedness to the SARs/SAEs before reporting. All SARs/SAEs should be assessed for seriousness, causality and expectedness.

For each SARs/SAEs, the following information will be collected:

- full details in medical terms with a diagnosis, if possible
- its duration (start and end dates; times, if applicable)
- action taken
- outcome
- causality, in the opinion of the investigator*
- whether the event would be considered expected or unexpected* (refer to Reference Safety Information)

*Assessment of causality and expectedness must be made by an obstetrician. If an obstetrician is unavailable, initial reports without causality and expectedness assessment should be submitted to Trial Office by a healthcare professional (i.e., HOLDS midwife) within 24 hours, but must be followed up by medical assessment as soon as possible thereafter, ideally within the following 24 hours.

The local Principle Investigator and others responsible for the woman's or baby's care should institute any supplementary investigations of SARs/SAEs based on their clinical judgement of the likely causative factors and provide further follow-up information as soon as available.

SARs/SAEs still present beyond 28 days post-partum must be followed up until the final outcome is determined.

Once reported to the Trial office initial assessment of causality and expectedness will be made by the CI and confirmed by one of the obstetrician or neonatal co-applicants. BCTU will report all SARs/SAEs to the DMC following a timetable agreed by the DMC prior to trial commencement. The DMC will review these open, unblinded data for safety. BCTU will also report all SARs/SAEs to the Sponsor, the MHRA and the REC annually, and to the Trial Steering Committee (TSC), blinded to treatment allocation following a timetable agreed by the TSC prior to trial commencement. Local Investigators are responsible for reporting SARs/SAEs to their host institution, according to local regulations, but they do not need to inform the REC as this will be done by BCTU as detailed above.

10.6 Reporting SUSARs

SAEs categorised by the local investigator as **both** suspected to be related to the trial drug **and** unexpected are SUSARs, and are subject to expedited reporting. All SUSARs must be recorded on the SAE Form and faxed to the BCTU on 0121 415 9136. Alternatively, the report can be emailed as a PDF attachment to the HOLDS email address from a NHS email account, within 24 hours of the research staff becoming aware of the event. The Chief Investigator (CI) or nominated individual will undertake urgent review of SUSARs within 24 hours of reporting and may request further information immediately from the patient's clinical team. The CI will not overrule the causality, expectedness or seriousness assessment given by the local investigator. If the CI disagrees with the local investigator's assessment, further clarification and discussion should take place to reach a consensus. If a consensus cannot be reached, both the opinion of the local investigator and the CI should be provided in the report to the MHRA and the REC.

The BCTU will report all SUSARs to the MHRA and the main REC. If the SUSAR resulted in death or was life-threatening this will be done within 7 days of the initial report being received or within 15 days for any other SUSAR. If information is incomplete at the time of initial reporting, or the event is ongoing, the BCTU will request follow-up information, including information for categorisation of causality, from the local investigator and will send the follow-up information to the MHRA and main REC within an additional 8 days for fatal or life-threatening SUSARs and as soon as possible for any other events.

10.7 Safety reporting responsibilities

10.7.1 Local Principal Investigator (or nominated individual in PI's absence)

- To record **all** safety events that occur in the women taking part in the trial. This includes serious, expected or unexpected adverse events, unless defined as outcomes above
- Medical judgement in assigning expectedness and causality to SAEs
- To fax SAE forms to BCTU within 24 hours of becoming aware, and to provide further follow-up information as soon as available
- To report SARs/SAEs to local committees if required, in line with local arrangements
- To sign an Investigator's Agreement accepting these responsibilities

10.7.2 Chief Investigator (or nominated individual in CI's absence)

- To assign initial causality and expected nature of SAEs where it has not been possible to obtain local assessment

- To review all events assessed as SAEs in the opinion of the local investigator for causality and expectedness and agree with obstetric/ neonatal co-applicants
- Alert the DMC Chair if concerned

10.7.3 Birmingham Clinical Trials Unit

- To prepare annual safety reports to the REC, TSC and MHRA
- To prepare SAE safety reports for the DMC following a timetable agreed by the DMC prior to trial commencement, or as requested by the DMC
- To report all fatal SAEs to the DMC for continuous safety review

10.7.4 Trial Steering Committee (TSC)

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

10.7.5 Data Monitoring Committee (DMC)

- To review (initially at approximately six-monthly intervals) overall safety and morbidity data to identify safety issues which may not be apparent on an individual case basis
- To recommend to the TSC whether the trial should continue unchanged, continue with protocol modifications, or stop

10.7.6 Sponsor

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

11 Data Management

11.1 Data collection forms

Data for the purpose of assessing the efficacy and safety within the HOLDS trial will be collected from the participating maternity units by the clinical team responsible for the participants care on a number of data collection (case report) forms (CRFs). Data required for the primary and the majority of secondary outcomes are objective measures which are routinely collected for clinical purposes and will be transcribed from woman's records, which collectively are the source data.

Paper forms will be used to confirm eligibility (prior to telephone randomisation), to document informed consent and to collect data during labour. The outcome data should be entered directly onto the database by those with on-line access. It can be completed in paper form and returned to the HOLDS Trial Office to be entered centrally onto the online database.

There is no need to hold any identifiable data in the Trial Office – the participating sites will collect the woman's NHS and hospital number and both may be used in the process of collecting missing data. The Trial Office will only have a unique identifier for the participant.

Data from the Case Report forms described earlier should be entered into the secure online HOLDS database as soon as possible after collection by the HOLDS research midwife or obstetrician. These clinical personnel will be allocated personal usernames and passwords that will only allow access to entry forms for the trial participants who are being treated at their site. Alternatively, paper forms can be sent to the HOLDS Trial Office for central input.

Data validation is built into the online database. Range, date and logic checks are performed at the point of data entry. Email reminders will be sent to the research midwives for missing data forms, missing data or data inconsistencies. This will be followed by phone contact.

11.2 Long-term storage of data

Storage will be authorised by BWNFT as Sponsor following submission of the end of trial report.

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

11.3 Definition of the End of Trial

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

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

12 Statistical methods and analysis

12.1 Sample size

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

12.2 Statistical analysis

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

Point estimates, 95% confidence intervals and p-values from two-sided tests will be calculated for all main outcome measures. Outcome will be adjusted for the minimisation variables. Analysis will be of all randomised subjects in the intention to treat population.

12.2.1 Primary Outcome Analysis

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

12.2.2 Secondary Outcome Analysis

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

12.2.3 Missing Data/Sensitivity Analyses

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

12.2.4 Subgroup Analyses

Subgroup analyses will be limited to degree of cervical dilation at recruitment (<=6m/>6cm). Tests for statistical heterogeneity will be performed prior to any examination of effect estimates with subgroups. The results of subgroup analyses will be treated with caution and used for the purposes of hypothesis generation only.

12.2.5 Interim Analyses

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

12.2.6 Final Analysis

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

13 Data access and quality assurance

13.1 Risk assessment

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

13.2 Confidentiality of personal data

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

Collaborating sites will store original consent and randomisation forms and all paper data collection forms and store them securely in the Site File (SF). These forms will be available to various regulatory bodies for inspection upon request. The consent and randomisation forms will be faxed or sent as attachments on emails between nhs.net email accounts, to the trial office, as these are the sole documents with identifiable details, again with consent from the participant. This will be used to perform in-house monitoring of the consent process.

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

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

13.3 In-house Data Quality Assurance

13.3.1 Monitoring and Audit

This trial will be regularly monitored by the sponsor to ensure compliance with GCP. A risk proportionate approach to the initiation, management and monitoring of the trial will be adopted and outlined in the trial-specific risk assessment. The sponsor will undertake a risk assessment prior to the trial commencing, which will be regularly reviewed based on trial progress, and monitoring findings. All sites will be informed of monitoring visits in advance. In addition BCTU will undertake remote monitoring as part of their Quality assurance checks

13.3.2 Direct Access to Source Data

Investigators and their host Trusts will be required to permit trial-related monitoring and audits to take place by the HOLDS Trial Coordinator and sponsor representative, providing direct access to

source data and documents as requested. The trial site may also be subject to audit by the Research and Development Office of their own Trust, or monitoring by the sponsor, and should do everything requested by the Chief Investigator in order to prepare and contribute to any inspection or audit. Trial participants will be made aware of the possibility of external audit of data they provide in the participant information sheet.

13.3.3 Definition of a serious breech

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

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

If a potential serious breach is identified by the Sponsor, Chief investigator, Principal Investigator or BCTU, the HOLDS Trial Office must be notified within 24 hours. It is the responsibility of the Chief Investigator and the sponsor to determine whether the incident constitutes a serious breach and if so, to assess the impact of the breach on the scientific value of the trial or the safety of participants. The sponsor will report serious breaches to the Research Ethics Committee and MHRA.

13.4 Trial Steering Committee

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

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

13.5 Data Monitoring Committee

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

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

and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results.

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

13.6 Project Management

Birmingham Women's NHS Foundation Trust (BWNFT) will be the trial sponsor and host organisation. Honorary contracts are in place with the University of Birmingham who employ the Chief Investigator (SK). Subcontracts will be put into place between the BWNFT and the other HEIs, detailing the budget resources allocated, the responsibilities and expected contributions of each party. Agreements with the clinical applicants will also be put into place.

Contracts will be agreed between BWNFT and the University of Aberdeen for the telephone randomisation system and with Sharps for the blinding, labelling, production and distribution of Syntocinon ®.

Day to day management will be undertaken by the Trial Co-ordinator with the Lead Midwife responsible for the sites. Weekly meetings will take place to monitor progress with the CI, Research Fellow and representatives from BCTU and the Sponsor as required. The full co-applicant group will meet at least quarterly.

13.7 Long-term storage of data

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

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

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

14 Organisation and responsibilities

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

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

14.1 Centre eligibility

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

- Complaint with current NICE Guidance for the care of nulliaprous women with delay in labour
- Use standard dose oxytocin regimen routinely
- Can offer extensive GCP cover- preferably 24/7
- A research active unit- with a track record of intrapartum research recruitment
- Ideally able to appoint HOLDS midwife from DS staff
- Can provide Pharmacy and Neonatal leads

14.2 Local Co-ordinator at each centre

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

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. In accordance with the principles of International Committee on Harmonisation Good Clinical Practice Guidelines (ICH GCP) the following areas listed in this section are also the responsibility of each Investigator. Responsibilities may be delegated to an appropriate member of trial site staff. Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable trial-related procedures. The listed responsibilities are:

- Ensure they are aware of the Data Protection Act, The Caldicott Principles and relevant Trust information policies
- Anonymise patient data where possible and hold it in accordance with the Data Protection Act.
- Consent must be sought before using the information for any other purpose
- Ensure they are aware of the Health and Safety act and Trust policy - including the implications for themselves and participants
- Report adverse events or suspected misconduct to the LREC and R&D Office
- Involve consumers in the research where possible.
- Keep the original signed consent form and information sheet secure
- Ensure completion and appropriate storage of all study related data collection forms
- Seek consent prior to recruitment if the patient is under the care of another health care professional

- Ensure that only researchers with a contractual relationship with the Trust hosting the research make contact with patients. There are procedures in place for issuing honorary contracts.
- Consider client diversity and be responsive to their information needs
- Keep participants up-to-date on the progress of the research and provide feedback at the end of the study
- Supply an annual report to the LREC and copy this to the R&D office.
- Monitor LREC approval dates to check approval is still valid
- Provide annual progress reports to R&D office
- Disseminate research findings to R&D Committee after completion (contractual obligations permitting) but prior to publication
- Able to arrange for secure storage of the trial related documents for 25 years

14.3 Research Midwife at each site

Each participating centre should also designate one midwife as local Midwife Coordinator, ideally based on Delivery Suite. They will be responsible for training staff, actively promoting the trial and maintaining the profile within each unit, troubleshooting challenges and collecting outcome data, to minimise the impact on busy clinical staff. Models will encompass part time research midwives and variable CLN support. Precise support will be tailored to each participating unit taking unit size into consideration. Contracts will only be continued if pre-specified numbers of women have been recruited. This midwife will be sent updates and newsletters, and will be invited to training and progress meetings approximately every six months.

14.4 Management of sites

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

14.5 Site set up and initiation

Start-up visits at each participating centre will be undertaken to before recruitment of women is permitted. At this visit Pharmacy arrangements will be explored. Recruitment cannot begin within any site until all required permissions are in place, training has been given, and women have received the antenatal letter regarding the trial.

Regular site visits will be made by the Lead Research Midwife (LRM)/CI/Research Fellow/ Sponsor representative/ Trial co-ordinator to ensure adherence to the protocol and to deal with any specific site issues. Regular study days will be undertaken to ensure that doctors and midwives involved with

the study are fully apprised of issues such as informed consent, data collection, follow-up, and changing regulations.

14.6 The HOLDS Trials Office at BCTU

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

14.7 Research Governance

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

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

The Trial Office will ensure researchers not employed by an NHS organisation hold an NHS honorary contract for that organisation.

14.8 Training in the Maternity Units

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

Training will be developed for all clinical staff within the maternity units to detail the trial purpose and processes so eligible women can be identified and given information about the trial. Training of clinical staff to agreed standards will be confirmed for each women recruited to the trial to monitor this. Recent guidance from the MHRA has suggested that those staff confirming eligibility and taking consent need to have appropriate GCP training. Once again this will be monitored centrally. To maximise recruitment over the 24 hour period as women may become eligible at any time, individual ways of ensuring this occurs will be developed with each centre and may involve such training being delivered as part of site set up.

The trial will use a cascade model whereby NIHR GCP facilitators alongside the Trial team will devise and deliver appropriate training to the PI and Research midwives in each centre. These staff will then ensure that this training is cascaded within units to all relevant clinical staff. This training will be updated and reviewed on a regular basis with regular refresher sessions for all involved.

15 Regulatory and Ethical Approval

15.1 Ethical and Trust Management Approval

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

The Trial Office is able to help the local Principal Investigator in the process of the site specific assessment by completing much of Site Specific Information section of the standard IRAS form as possible. The local Principal Investigator will be responsible for liaison with the Trust management with respect to locality issues and obtaining the necessary signatures at their Trust.

As soon as Trust approval has been obtained, the Trial Office will send a folder containing all trial materials to the local Principal Investigator. Potential trial participants can then start to be approached. Face to face Site Initiation visits will be undertaken before recruitment begins.

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

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

15.2 Funding and Cost implications

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

The trial has been designed to minimise extra 'service support' costs for participating hospitals, with no extra visits to hospital and no extra tests. Additional costs service support costs associated with the trial, e.g. identifying potential participants, gaining consent, are estimated in the Site Specific Information section of the standard IRAS form. These costs should be met by accessing the Trust's Support for Science budget *via* the Local Comprehensive Research Network.

15.3 Indemnity

This is a clinician-initiated trial. The Sponsor (the BWNFT) holds the relevant insurance for Clinical Trials (negligent harm). Participants may be able to claim compensation, if they can prove that the BWNFT has been negligent. However, as this clinical trial is being carried out in a hospital setting, NHS Trusts, NHS health Boards and Non-Trust Hospitals have a duty of care to the patients 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 BWNFT, upon request.

16 Public and Patient Involvement

16.1 The aims of active involvement in this project

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

Parents and Researchers Involvement in Maternity and Early pregnancy (PRIME) group, a PPI group set up in collaboration with the University of Birmingham Collaboration for Leadership and Applied Health Research and Care (CLAHRC) and has a geographical and socio-economically diverse spectrum of women with experience of Maternity Services use and their partners. They will review the trial documentation prior to the start of the trial and our intention is to regularly update them with progress (both successes and challenges) and to invite PPI involvement in staff training regarding the approach and discussion of the trial.

As described earlier the HOLDS website with hyperlinks to NCT home page will make full use of social networking platforms like Twitter and Facebook in the form of a HOLDS page and a HOLDS-PPI group - subject to REC approval. This will facilitate dissemination, communication and in our experience, recruitment. We will publish project progress and results through press releases from our University, HTA website and the project website.

16.2 A description of the methods of involvement

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

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

17 Intellectual Property

Oxytocin is currently marketed in the UK by Novartis amongst other pharmaceutical companies as it is a generic medicine. It would be appropriate to engage with these companies at the end of the study to determine whether or not they have any interest in exploiting the clinical data generated in relation to the extended use to high dose oxytocin.

The contractor is Birmingham Women's NHS Foundation Trust (BWNFT) who will own all IP. A collaboration agreement will be put in place between UoB and BWNFT regarding the project and the sharing between the parties of any benefit realised from the arising IP. This will be drafted and in place prior to the commencement of the Grant.

18 Reporting, publications and notification of results

18.1 Authorship policy

Ownership of the data arising from this trial resides with the grant holders. On completion of the trial, the trial data will be analysed and tabulated, and a final trial report prepared for the NIHR. A writing committee may be established to prepare the report and any subsequent papers.

Authorship will be based on the four criteria adopted by the BMJ

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The main report of the trial will be published in the name of the HOLDS Collaborative Group, acknowledging the writing group as authors. Subsequent publications should also be published in the HOLDS Collaborative Group name, but those academics who contribute to specific aspects may be listed as authors.

18.2 Publication

A meeting will be held after the end of the trial to allow discussion of the main results among the collaborators prior to publication. The success of the trial depends entirely on the wholehearted collaboration of a large number of clinicians, midwives and others. For this reason, chief credit for the main results will be given not to the committees or central organisers but to all those who have collaborated in the trial. Centres will be permitted to publish data obtained from participants in the HOLDS Trial that use Trial outcome measures but do not relate to the trial randomised evaluation and hypothesis.

18.3 Ancillary studies

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

19 History of Amendments to Protocol

24th February 2016

Response to review by the Ethics Committee

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

Substantial Amendment 1: 16th August 2016

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

20 References

1 Kenyon S, Armstrong N, Johnson T, Walkinshaw S, Petrou S, Howman A, Cheed V, Markham C, McNicol S, Willars J, Waugh J. (2013) Standard or high dose oxytocin for nulliparous women with confirmed delay in labour: quantitative and qualitative results from a pilot randomised controlled trial. British Journal of Obstetrics and Gynaecology; 120(11):1403-12. DOI 10.1111/1471-0528.12331

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9 Wei SQ, Luo ZC, Qi HP, Xu H, Fraser WD. (2010) High-dose vs low-dose oxytocin for labor augmentation: a systematic review. American Journal of Obstetrics and Gynecology; 203:296–304. DOI 10.1016/j.ajog.2010.03.007.

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11 American College of Obstetricians and Gynecologists (2014) Safe prevention of the primary cesarean delivery. Obstetric Care Consensus No. 1. Obstet. Gynecol;123: 693-711. DOI 10.1097/01.AOG.0000444441.04111.1d.

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13 Cohen WR, Friedman EA. (2015) Perils of new labor management guidelines. AJOG. 212, Issue 4, 420–427. DOI 10.1016/j.ajog.2014.09.008

14 Personal communication from Dr Mairead Black, Aberdeen

21 Appendices

1. SPC: Syntocinon 5 IU/ml Concentrate for solution for infusion

2. SPC: Syntocinon 10 IU/ml Concentrate for solution for infusion

21.1 Appendix One: SPC: Syntocinon 5 IU/ml Concentrate for solution for infusion

Summary of Product Characteristics

Syntocinon 5 IU/ml Concentrate for solution for infusion

1. NAME OF THE MEDICINAL PRODUCT

Syntocinon® 5 IU/ml Concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxytocin.

Concentrate for solution for infusion (in 1mL ampoule) containing 5 IU/mL

Excipient(s) with known effect:
Ethanol 5.000mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

A clear, colourless, sterile solution in 1ml clear glass ampoules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Antepartum
- Induction of labour for medical reasons, e.g. in cases of post-term gestation, premature rupture of the membranes, pregnancy-induced hypertension (pre-eclampsia)
- Stimulation of labour in hypotonic uterine inertia
- Early stages of pregnancy as adjunctive therapy for the management of incomplete, inevitable, or missed abortion.

Postpartum
- During caesarean section, but following delivery of the child
- Prevention and treatment of postpartum uterine atony and haemorrhage

4.2 Posology and method of administration

Induction or enhancement of labour: Oxytocin should not be started for 6 hours following administration of vaginal prostaglandins. Syntocinon should be administered as an intravenous

(i.v.) drip infusion or, preferably, by means of a variable-speed infusion pump. For drip infusion it is recommended that 5 IU of Syntocinon be added to 500ml of a physiological electrolyte solution (such as sodium chloride 0.9%). For patients in whom infusion of sodium chloride must be avoided, 5% dextrose solution may be used as the diluent (see Section 4.4 “Special warnings and precautions for use”). To ensure even mixing, the bottle or bag must be turned upside down several times before use.

The initial infusion rate should be set at 1 to 4 milliunits/minute (2 to 8 drops/minute). It may be gradually increased at intervals not shorter than 20 minutes and increments of not more than 1-2 milliunits/minute, until a contraction pattern similar to that of normal labour is established. In pregnancy near term this can often be achieved with an infusion of less than 10 milliunits/minute (20 drops/minute), and the recommended maximum rate is 20 milliunits/minute (40 drops/minute). In the unusual event that higher rates are required, as may occur in the management of foetal death *in utero* or for induction of labour at an earlier stage of pregnancy, when the uterus is less sensitive to oxytocin, it is advisable to use a more concentrated Syntocinon solution, e.g., 10 IU in 500ml.

When using a motor-driven infusion pump which delivers smaller volumes than those given by drip infusion, the concentration suitable for infusion within the recommended dosage range must be calculated according to the specifications of the pump.

The frequency, strength, and duration of contractions as well as the foetal heart rate must be carefully monitored throughout the infusion. Once an adequate level of uterine activity is attained, aiming for 3 to 4 contractions every 10 minutes, the infusion rate can often be reduced. In the event of uterine hyperactivity and/or foetal distress, the infusion must be discontinued immediately.

If, in women who are at term or near term, regular contractions are not established after the infusion of a total amount of 5 IU, it is recommended that the attempt to induce labour be ceased; it may be repeated on the following day, starting again from a rate of 1 to 4 milliunits/minute (see Section 4.3 “Contra-indications”).

Incomplete, inevitable, or missed abortion: 5 IU by i.v. infusion (5 IU diluted in physiological electrolyte solution and administered as an i.v. drip infusion or, preferably, by means of a variable-speed infusion pump over 5 minutes), if necessary followed by i.v. infusion at a rate of 20 to 40 milliunits/minute.

Caesarean section: 5 IU by i.v. infusion (5 IU diluted in physiological electrolyte solution and administered as an i.v. drip infusion or, preferably, by means of a variable-speed infusion pump over 5 minutes) immediately after delivery.

Prevention of postpartum uterine haemorrhage: The usual dose is 5 IU by i.v. infusion (5 IU diluted in physiological electrolyte solution and administered as an i.v. drip infusion or, preferably, by means of a variable-speed infusion pump over 5 minutes) after delivery of the placenta. In women given Syntocinon for induction or enhancement of labour, the infusion should be continued at an increased rate during the third stage of labour and for the next few hours thereafter.

Treatment of postpartum uterine haemorrhage: 5 IU by i.v. infusion (5 IU diluted in physiological electrolyte solution and administered as an i.v. drip infusion or, preferably, by means of a variable-speed infusion pump over 5 minutes), followed in severe cases by i.v. infusion of a solution containing 5 to 20 IU of oxytocin in 500ml of an electrolyte-containing diluent, run at the rate necessary to control uterine atony.

Route of administration: Intravenous infusion.

Special populations

Renal impairment
No studies have been performed in renally impaired patients.

Hepatic impairment
No studies have been performed in hepatically impaired patients.

Paediatric population
No studies have been performed in paediatric patients.

Elderly population
No studies have been performed in elderly patients (65 years old and over).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Hypertonic uterine contractions, mechanical obstruction to delivery, foetal distress.

Any condition in which, for foetal or maternal reasons, spontaneous labour is inadvisable and/or vaginal delivery is contra-indicated: e.g.:

- Significant cephalopelvic disproportion
- Foetal 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 resulting from major surgery including classical caesarean section.

Syntocinon should not be used for prolonged periods in patients with oxytocin-resistant uterine inertia, severe pre-eclamptic toxaemia or severe cardiovascular disorders.

Syntocinon must not be administered within 6 hours after vaginal prostaglandins have been given (see section 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use

Syntocinon must only be administered as an i.v. infusion and never by i.v. bolus injection as it may cause an acute short-lasting hypotension accompanied with flushing and reflex tachycardia.

Induction of labour
The induction of labour by means of oxytocin should be attempted only when strictly indicated for medical reasons. Administration should only be under hospital conditions and qualified medical supervision.

Cardiovascular disorders
Syntocinon should be used with caution in patients who have a pre-disposition to myocardial ischaemia due to pre-existing cardiovascular disease (such as hypertrophic cardiomyopathy,

valvular heart disease and/or ischaemic heart disease including coronary artery vasospasm), to avoid significant changes in blood pressure and heart rate in these patients.

QT Syndrome
Syntocinon should be given with caution to patients with known 'long QT syndrome' or related symptoms and to patients taking drugs that are known to prolong the QTc interval (see section 4.5 Interaction with other medicinal products and other forms of interaction).

When Syntocinon is given for induction and enhancement of labour:

- Foetal distress and foetal death: Administration of oxytocin at excessive doses results in uterine overstimulation which may cause foetal distress, asphyxia and death, or may lead to hypertonicity, tetanic contractions or rupture of the uterus. Careful monitoring of foetal heart rate and uterine motility (frequency, strength, and duration of contractions) is essential, so that the dosage may be adjusted to individual response.
- Particular caution is required in the presence of borderline cephalopelvic disproportion, secondary uterine inertia, mild or moderate degrees of pregnancy-induced hypertension or cardiac disease, and in patients above 35 years of age or with a history of lower-uterine-segment caesarean section.
- Disseminated intravascular coagulation: In rare circumstances, the pharmacological induction of labour using uterotonic agents, including oxytocin increases the risk of post partum disseminated intravascular coagulation (DIC). The pharmacological induction itself and not a particular agent is linked to such risk. This risk is increased in particular if the woman has additional risk factors for DIC such as being 35 years of age or over, complications during pregnancy and gestational age more than 40 weeks. In these women, oxytocin or any other alternative drug should be used with care, and the practitioner should be alerted by signs of DIC.

Intrauterine death
In the case of foetal death *in utero*, and/or in the presence of meconium-stained amniotic fluid, tumultuous labour must be avoided, as it may cause amniotic fluid embolism.

Water intoxication
Because oxytocin possesses slight antidiuretic activity, its prolonged i.v. administration at high doses in conjunction with large volumes of fluid, as may be the case in the treatment of inevitable or missed abortion or in the management of postpartum haemorrhage, may cause water intoxication associated with hyponatraemia. The combined antidiuretic effect of oxytocin and the i.v. fluid administration may cause fluid overload leading to a haemodynamic form of acute pulmonary oedema without hyponatraemia. To avoid these rare complications, the following precautions must be observed whenever high doses of oxytocin are administered over a long time: an electrolyte-containing diluent must be used (not dextrose); the volume of infused fluid should be kept low (by infusing oxytocin at a higher concentration than recommended for the induction or enhancement of labour at term); fluid intake by mouth must be restricted; a fluid balance chart should be kept, and serum electrolytes should be measured when electrolyte imbalance is suspected.

Renal impairment

Caution should be exercised in patients with severe renal impairment because of possible water retention and possible accumulation of oxytocin (see section 5.2 Pharmacokinetics).

4.5 Interaction with other medicinal products and other forms of interaction

Interaction resulting in a concomitant use not recommended

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 (see section 4.3 Contraindications).

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 (see section 4.4 Special warnings and precautions for use).

Interactions 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.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with oxytocin. Based on the wide experience with this drug and its chemical structure and pharmacological properties, it is not expected to present a risk of foetal abnormalities when used as indicated.

Oxytocin may be found in small quantities in mother's breast milk. However, oxytocin is not expected to cause harmful effects in the newborn because it passes into the alimentary tract where it undergoes rapid inactivation.

4.7 Effects on ability to drive and use machines

Syntocinon can induce labour, therefore caution should be exercised when driving or operating machines. Women with uterine contractions should not drive or use machines.

4.8 Undesirable effects

As there is a wide variation in uterine sensitivity, uterine spasm may be caused in some instances by what are normally considered to be low doses. When oxytocin is used by i.v. infusion for the induction or enhancement of labour, administration at too high doses results in uterine overstimulation which may cause foetal distress, asphyxia, and death, or may lead to hypertonicity, tetanic contractions, soft tissue damage or rupture of the uterus.

Rapid i.v. bolus injection of oxytocin at doses amounting to several IU may result in acute short-lasting hypotension accompanied with flushing and reflex tachycardia (see section 4.4 Special warnings and precautions for use). These rapid haemodynamic changes may result in myocardial

ischaemia, particularly in patients with pre-existing cardiovascular disease. Rapid i.v. bolus injection of oxytocin at doses amounting to several IU may also lead to QTc prolongation.

In rare circumstances the pharmacological induction of labour using uterotonic agents, including oxytocin, increases the risk of postpartum disseminated intravascular coagulation (see section 4.4 Special warnings and precautions for use).

Water intoxication
Water intoxication associated with maternal and neonatal hyponatraemia has been reported in cases where high doses of oxytocin together with large amounts of electrolyte-free fluid have been administered over a prolonged period of time (see Section 4.4 "Special warnings and precautions for use"). The combined antidiuretic effect of oxytocin and the i.v. fluid administration may cause fluid overload leading to a haemodynamic form of acute pulmonary oedema without hyponatraemia (see section 4.4. Special warnings and precautions for use).

Symptoms of water intoxication include:

1. Headache, anorexia, nausea, vomiting and abdominal pain.

2. Lethargy, drowsiness, unconsciousness and grand-mal type seizures.

3. Low blood electrolyte concentration.

Undesirable effects (Tables 1 and 2) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), including isolated reports; not known (cannot be estimated from the available data).The ADRs tabulated below are based on clinical trial results as well as postmarketing reports.

The adverse drug reactions derived from post-marketing experience with Syntocinon are via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 1 Adverse drug reactions in mother

System organ class	Adverse drug reaction
Immune system disorders	Rare: Anaphylactic/ Anaphylactoid reaction associated with dyspnoea, hypotension or Shock
Nervous system disorders	Common: Headache
Cardiac disorders	Common Tachycardia, bradycardia Uncommon: Arrhythmia Not known: Myocardial ischaemia, Electrocardiogram QTc prolongation
Vascular disorders	Not known: Hypotension, haemorrhage
Gastrointestinal disorders	Common: Nausea, vomiting
Skin and subcutaneous tissue disorders	Rare: Rash
Pregnancy, puerperium and perinatal conditions	Not known: Uterine hypertonus, tetanic contractions of the uterus, rupture of the uterus
Metabolism and nutrition disorders	Not known: Water intoxication, maternal hyponatraemia

Respiratory, thoracic and mediastinal disorders	Not known: acute pulmonary oedema
General disorders and administration site conditions	Not known: Flushing
Blood and lymphatic system disorders	Not known: disseminated intravascular coagulation
Skin and subcutaneous tissue disorder	Not known: Angioedema

Table 2 Adverse drug reactions in foetus/neonate

System organ class	Adverse drug reaction
Pregnancy, puerperium and perinatal conditions	Not known: foetal distress, asphyxia and death
Metabolism and nutrition disorders	Not known: Neonatal hyponatraemia

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorisation of a medicinal product is important. It allows continued monitoring of the benefit/risk balance of a medicinal product. Healthcare professions are asked to report any adverse reactions via Yellow Card Scheme (www.mhra.gov.uk/yellowcard)

4.9 Overdose

The fatal dose of Syntocinon has not been established. Syntocinon is subject to inactivation by proteolytic enzymes of the alimentary tract. Hence it is not absorbed from the intestine and is not likely to have toxic effects when ingested.

The symptoms and consequences of overdosage are those mentioned under sections 4.4 “Special warnings and precautions for use” and 4.8 “Undesirable effects”. In addition, as a result of uterine overstimulation, placental abruption and/or amniotic fluid embolism have been reported.

Treatment: When signs or symptoms of overdosage occur during continuous i.v. administration of Syntocinon, the infusion must be discontinued at once and oxygen should be given to the mother. In cases of water intoxication it is essential to restrict fluid intake, promote diuresis, correct electrolyte imbalance, and control convulsions that may eventually occur. In the case of coma, a free airway should be maintained with routine measures normally employed in the nursing of the unconscious patient.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Posterior pituitary lobe hormones
ATC code: H01B B02

Mechanism of action
Oxytocin is a cyclic nonapeptide that is obtained by chemical synthesis. This synthetic form is identical to the natural hormone that is stored in the posterior pituitary and released into the systemic circulation in response to suckling and labour.

Oxytocin stimulates the smooth muscle of the uterus, more powerfully towards the end of pregnancy, during labour, and immediately postpartum. At these times, the oxytocin receptors in the myometrium are increased.

The oxytocin receptors are G-proteins coupled receptors. Activation of receptor by oxytocin triggers release of calcium from intracellular stores and thus leads to myometrial contraction.

Oxytocin elicits rhythmic contractions in upper segment of uterus, similar in frequency, force and duration to those observed during labour.

Being synthetic, oxytocin in Syntocinon does not contain vasopressin, but even in its pure form oxytocin possesses some weak intrinsic vasopressin-like antidiuretic activity.

Based on in vitro studies, prolonged exposure of oxytocin had been reported to cause desensitisation of oxytocin receptors probably due to down-regulation of oxytocin-binding sites, destabilisation of oxytocin receptors mRNA and internalisation of oxytocin receptors.

Plasma levels and onset/duration of effect
Intravenous infusion. When Syntocinon is given by continuous i.v. infusion at doses appropriate for induction or enhancement of labour, the uterine response sets in gradually and usually reaches a steady state within 20 to 40 minutes. The corresponding plasma levels of oxytocin are comparable to those measured during spontaneous first-stage labour. For example, oxytocin plasma levels in 10 pregnant women at term receiving a 4 milliunits per minute intravenous infusion were 2 to 5 microunits/mL. Upon discontinuation of the infusion, or following a substantial reduction in the infusion rate, e.g. in the event of overstimulation, uterine activity declines rapidly but may continue at an adequate lower level.

5.2 Pharmacokinetic properties

Absorption
Plasma levels of oxytocin following intravenous infusion at 4 milliunits per minute in pregnant women at term were 2 to 5 microunits/mL.

Distribution
The steady-state volume of distribution determined in 6 healthy men after i.v. injection is 12.2 L or 0.17 L/kg. Plasma protein binding is negligible for oxytocin. It crosses the placenta in both directions. Oxytocin may be found in small quantities in mother's breast milk.

Biotransformation/Metabolism
Oxytocinase is a glycoprotein aminopeptidase that is produced during pregnancy and appears in the plasma. It is capable of degrading oxytocin. It is produced from both the mother and the foetus. Liver and kidney plays a major role in metabolising and clearing oxytocin from the plasma. Thus, liver, kidney and systemic circulation contribute to the biotransformation of oxytocin.

Elimination
Plasma half-life of oxytocin ranges from 3 to 20 min. The metabolites are excreted in urine

whereas less than 1% of the oxytocin is excreted unchanged in urine. The metabolic clearance rate amounts to 20 mL/kg/ min in the pregnant woman.

Renal impairment
No studies have been performed in renally impaired patients. However, considering the excretion of oxytocin and its reduced urinary excretion because of anti-diuretic properties, the possible accumulation of oxytocin can result in prolonged action.

Hepatic impairment
No studies have been performed in hepatically impaired patients. Pharmacokinetic alteration in patients with impaired hepatic function is unlikely since metabolising enzyme, oxytocinase, is not confined to liver alone and the oxytocinase levels in placenta during the term has significantly increased. Therefore, biotransformation of oxytocin in impaired hepatic function may not result in substantial changes in metabolic clearance of oxytocin.

5.3 Preclinical safety data

Pre-clinical data for oxytocin reveal no special hazard for humans based on conventional studies of single dose acute toxicity, genotoxicity, and mutagenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate tri-hydrate, acetic acid, chlorobutanol, ethanol and water for injections.

6.2 Incompatibilities

Syntocinon should not be infused via the same apparatus as blood or plasma, because the peptide linkages are rapidly inactivated by oxytocin-inactivating enzymes. Syntocinon is incompatible with solutions containing sodium metabisulphite as a stabiliser.

6.3 Shelf life

Five years

6.4 Special precautions for storage

Store between 2°C and 8°C. May be stored up to 30°C for 3 months, but must then be discarded.

6.5 Nature and contents of container

Clear glass 1 ml ampoules. Boxes of 5 ampoules.

6.6 Special precautions for disposal and other handling

Snap ampoules: no file required.

Syntocinon is compatible with the following infusion fluids, but due attention should be paid to the advisability of using electrolyte fluids in individual patients: sodium/potassium chloride (103mmol Na^+ and 51mmol K^+), sodium bicarbonate 1.39%, sodium chloride 0.9%, sodium lactate 1.72%, dextrose 5%, laevulose 20%, macrodex 6%, rheomacrodex 10%, Ringer's solution.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 03 October 1977

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18th February 2016

21.2 Appendix Two: SPC: Syntocinon 10 IU/ml Concentrate for solution for infusion

Summary of Product Characteristics

Syntocinon 10 IU/ml Concentrate for solution for infusion

1. NAME OF THE MEDICINAL PRODUCT

Syntocinon® 10 IU/ml Concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxytocin.

Concentrate for solution for infusion (in 1mL ampoule) containing 10 IU/mL

Excipient(s) with known effect:
Ethanol 5.000mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

A clear, colourless, sterile solution in 1ml clear glass ampoules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Antepartum
- Induction of labour for medical reasons, e.g. in cases of post-term gestation, premature rupture of the membranes, pregnancy-induced hypertension (pre-eclampsia)
- Stimulation of labour in hypotonic uterine inertia
- Early stages of pregnancy as adjunctive therapy for the management of incomplete, inevitable, or missed abortion.

Postpartum
- During caesarean section, but following delivery of the child
- Prevention and treatment of postpartum uterine atony and haemorrhage

4.2 Posology and method of administration

Induction or enhancement of labour: Oxytocin should not be started for 6 hours following administration of vaginal prostaglandins. Syntocinon should be administered as an intravenous

(i.v.) drip infusion or, preferably, by means of a variable-speed infusion pump. For drip infusion it is recommended that 5 IU of Syntocinon be added to 500ml of a physiological electrolyte solution (such as sodium chloride 0.9%). For patients in whom infusion of sodium chloride must be avoided, 5% dextrose solution may be used as the diluent (see Section 4.4 “Special warnings and precautions for use”). To ensure even mixing, the bottle or bag must be turned upside down several times before use.

The initial infusion rate should be set at 1 to 4 milliunits/minute (2 to 8 drops/minute). It may be gradually increased at intervals not shorter than 20 minutes and increments of not more than 1-2 milliunits/minute, until a contraction pattern similar to that of normal labour is established. In pregnancy near term this can often be achieved with an infusion of less than 10 milliunits/minute (20 drops/minute), and the recommended maximum rate is 20 milliunits/minute (40 drops/minute). In the unusual event that higher rates are required, as may occur in the management of foetal death *in utero* or for induction of labour at an earlier stage of pregnancy, when the uterus is less sensitive to oxytocin, it is advisable to use a more concentrated Syntocinon solution, e.g., 10 IU in 500ml.

When using a motor-driven infusion pump which delivers smaller volumes than those given by drip infusion, the concentration suitable for infusion within the recommended dosage range must be calculated according to the specifications of the pump.

The frequency, strength, and duration of contractions as well as the foetal heart rate must be carefully monitored throughout the infusion. Once an adequate level of uterine activity is attained, aiming for 3 to 4 contractions every 10 minutes, the infusion rate can often be reduced. In the event of uterine hyperactivity and/or foetal distress, the infusion must be discontinued immediately.

If, in women who are at term or near term, regular contractions are not established after the infusion of a total amount of 5 IU, it is recommended that the attempt to induce labour be ceased; it may be repeated on the following day, starting again from a rate of 1 to 4 milliunits/minute (see Section 4.3 “Contra-indications”).

Incomplete, inevitable, or missed abortion: 5 IU by i.v. infusion (5 IU diluted in physiological electrolyte solution and administered as an i.v. drip infusion or, preferably, by means of a variable-speed infusion pump over 5 minutes), if necessary followed by i.v. infusion at a rate of 20 to 40 milliunits/minute.

Caesarean section: 5 IU by i.v. infusion (5 IU diluted in physiological electrolyte solution and administered as an i.v. drip infusion or, preferably, by means of a variable-speed infusion pump over 5 minutes) immediately after delivery.

Prevention of postpartum uterine haemorrhage: The usual dose is 5 IU by i.v. infusion (5 IU diluted in physiological electrolyte solution and administered as an i.v. drip infusion or, preferably, by means of a variable-speed infusion pump over 5 minutes) after delivery of the placenta. In women given Syntocinon for induction or enhancement of labour, the infusion should be continued at an increased rate during the third stage of labour and for the next few hours thereafter.

Treatment of postpartum uterine haemorrhage: 5 IU by i.v. infusion (5 IU diluted in physiological electrolyte solution and administered as an i.v. drip infusion or, preferably, by means of a variable-speed infusion pump over 5 minutes), followed in severe cases by i.v. infusion of a solution containing 5 to 20 IU of oxytocin in 500ml of an electrolyte-containing diluent, run at the rate necessary to control uterine atony.

Route of administration: Intravenous infusion.

Special populations

Renal impairment
No studies have been performed in renally impaired patients.

Hepatic impairment
No studies have been performed in hepatically impaired patients.

Paediatric population
No studies have been performed in paediatric patients.

Elderly population
No studies have been performed in elderly patients (65 years old and over).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Hypertonic uterine contractions, mechanical obstruction to delivery, foetal distress.

Any condition in which, for foetal or maternal reasons, spontaneous labour is inadvisable and/or vaginal delivery is contra-indicated: e.g.:

- Significant cephalopelvic disproportion
- Foetal 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 resulting from major surgery including classical caesarean section.

Syntocinon should not be used for prolonged periods in patients with oxytocin-resistant uterine inertia, severe pre-eclamptic toxaemia or severe cardiovascular disorders.

Syntocinon must not be administered within 6 hours after vaginal prostaglandins have been given (see section 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use

Syntocinon must only be administered as an i.v. infusion and never by i.v. bolus injection as it may cause an acute short-lasting hypotension accompanied with flushing and reflex tachycardia.

Induction of labour
The induction of labour by means of oxytocin should be attempted only when strictly indicated for medical reasons. Administration should only be under hospital conditions and qualified medical supervision.

Cardiovascular disorders
Syntocinon should be used with caution in patients who have a pre-disposition to myocardial ischaemia due to pre-existing cardiovascular disease (such as hypertrophic cardiomyopathy,

valvular heart disease and/or ischaemic heart disease including coronary artery vasospasm), to avoid significant changes in blood pressure and heart rate in these patients.

QT Syndrome
Syntocinon should be given with caution to patients with known 'long QT syndrome' or related symptoms and to patients taking drugs that are known to prolong the QTc interval (see section 4.5 Interaction with other medicinal products and other forms of interaction).

When Syntocinon is given for induction and enhancement of labour:

- Foetal distress and foetal death: Administration of oxytocin at excessive doses results in uterine overstimulation which may cause foetal distress, asphyxia and death, or may lead to hypertonicity, tetanic contractions or rupture of the uterus. Careful monitoring of foetal heart rate and uterine motility (frequency, strength, and duration of contractions) is essential, so that the dosage may be adjusted to individual response.
- Particular caution is required in the presence of borderline cephalopelvic disproportion, secondary uterine inertia, mild or moderate degrees of pregnancy-induced hypertension or cardiac disease, and in patients above 35 years of age or with a history of lower-uterine-segment caesarean section.
- Disseminated intravascular coagulation: In rare circumstances, the pharmacological induction of labour using uterotonic agents, including oxytocin increases the risk of post partum disseminated intravascular coagulation (DIC). The pharmacological induction itself and not a particular agent is linked to such risk. This risk is increased in particular if the woman has additional risk factors for DIC such as being 35 years of age or over, complications during pregnancy and gestational age more than 40 weeks. In these women, oxytocin or any other alternative drug should be used with care, and the practitioner should be alerted by signs of DIC.

Intrauterine death
In the case of foetal death *in utero*, and/or in the presence of meconium-stained amniotic fluid, tumultuous labour must be avoided, as it may cause amniotic fluid embolism.

Water intoxication
Because oxytocin possesses slight antidiuretic activity, its prolonged i.v. administration at high doses in conjunction with large volumes of fluid, as may be the case in the treatment of inevitable or missed abortion or in the management of postpartum haemorrhage, may cause water intoxication associated with hyponatraemia. The combined antidiuretic effect of oxytocin and the i.v. fluid administration may cause fluid overload leading to a haemodynamic form of acute pulmonary oedema without hyponatraemia. To avoid these rare complications, the following precautions must be observed whenever high doses of oxytocin are administered over a long time: an electrolyte-containing diluent must be used (not dextrose); the volume of infused fluid should be kept low (by infusing oxytocin at a higher concentration than recommended for the induction or enhancement of labour at term); fluid intake by mouth must be restricted; a fluid balance chart should be kept, and serum electrolytes should be measured when electrolyte imbalance is suspected.

Renal impairment

Caution should be exercised in patients with severe renal impairment because of possible water retention and possible accumulation of oxytocin (see section 5.2 Pharmacokinetics).

4.5 Interaction with other medicinal products and other forms of interaction

Interaction resulting in a concomitant use not recommended

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 (see section 4.3 Contraindications).

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 (see section 4.4 Special warnings and precautions for use).

Interactions 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.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with oxytocin. Based on the wide experience with this drug and its chemical structure and pharmacological properties, it is not expected to present a risk of foetal abnormalities when used as indicated.

Oxytocin may be found in small quantities in mother's breast milk. However, oxytocin is not expected to cause harmful effects in the newborn because it passes into the alimentary tract where it undergoes rapid inactivation.

4.7 Effects on ability to drive and use machines

Syntocinon can induce labour, therefore caution should be exercised when driving or operating machines. Women with uterine contractions should not drive or use machines.

4.8 Undesirable effects

As there is a wide variation in uterine sensitivity, uterine spasm may be caused in some instances by what are normally considered to be low doses. When oxytocin is used by i.v. infusion for the induction or enhancement of labour, administration at too high doses results in uterine overstimulation which may cause foetal distress, asphyxia, and death, or may lead to hypertonicity, tetanic contractions, soft tissue damage or rupture of the uterus.

Rapid i.v. bolus injection of oxytocin at doses amounting to several IU may result in acute short-lasting hypotension accompanied with flushing and reflex tachycardia (see section 4.4 Special warnings and precautions for use). These rapid haemodynamic changes may result in myocardial

ischaemia, particularly in patients with pre-existing cardiovascular disease. Rapid i.v. bolus injection of oxytocin at doses amounting to several IU may also lead to QTc prolongation.

In rare circumstances the pharmacological induction of labour using uterotonic agents, including oxytocin, increases the risk of postpartum disseminated intravascular coagulation (see section 4.4 Special warnings and precautions for use).

Water intoxication
Water intoxication associated with maternal and neonatal hyponatraemia has been reported in cases where high doses of oxytocin together with large amounts of electrolyte-free fluid have been administered over a prolonged period of time (see Section 4.4 “Special warnings and precautions for use”). The combined antidiuretic effect of oxytocin and the i.v. fluid administration may cause fluid overload leading to a haemodynamic form of acute pulmonary oedema without hyponatraemia (see section 4.4. Special warnings and precautions for use).

Symptoms of water intoxication include:

1. Headache, anorexia, nausea, vomiting and abdominal pain.

2. Lethargy, drowsiness, unconsciousness and grand-mal type seizures.

3. Low blood electrolyte concentration.

Undesirable effects (Tables 1 and 2) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), including isolated reports; not known (cannot be estimated from the available data).The ADRs tabulated below are based on clinical trial results as well as postmarketing reports.

The adverse drug reactions derived from post-marketing experience with Syntocinon are via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 1 Adverse drug reactions in mother

System organ class	Adverse drug reaction
Immune system disorders	Rare: Anaphylactic/ Anaphylactoid reaction associated with dyspnoea, hypotension or Shock
Nervous system disorders	Common: Headache
Cardiac disorders	Common Tachycardia, bradycardia Uncommon: Arrhythmia Not known: Myocardial ischaemia, Electrocardigram QTc prolongation
Vascular disorders	Not known: Hypotension, haemorrhage
Gastrointestinal disorders	Common: Nausea, vomiting
Skin and subcutaneous tissue disorders	Rare: Rash
Pregnancy, puerperium and perinatal conditions	Not known: Uterine hypertonus, tetanic contractions of uterus, rupture of the uterus
Metabolism and nutrition disorders	Not known: Water intoxication, maternal hyponatraemia

Respiratory, thoracic and mediastinal disorders	Not known: acute pulmonary oedema
General disorders and administration site conditions	Not known: Flushing
Blood and lymphatic system disorders	Not known: disseminated intravascular coagulation
Skin and subcutaneous tissue disorders	Not known: Angioedema

Table 2 Adverse drug reactions in foetus/neonate

System organ class	Adverse drug reaction
Pregnancy, puerperium and perinatal conditions	Not known: foetal distress, asphyxia and death
Metabolism and nutrition disorders	Not known: Neonatal hyponatraemia

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorisation of a medicinal product is important. It allows continued monitoring of the benefit/risk balance of a medicinal product. Healthcare professions are asked to report any adverse reactions via Yellow Card Scheme (www.mhra.gov.uk/yellowcard)

4.9 Overdose

The fatal dose of Syntocinon has not been established. Syntocinon is subject to inactivation by proteolytic enzymes of the alimentary tract. Hence it is not absorbed from the intestine and is not likely to have toxic effects when ingested.

The symptoms and consequences of overdosage are those mentioned under sections 4.4 “Special warnings and precautions for use” and 4.8 “Undesirable effects”. In addition, as a result of uterine overstimulation, placental abruption and/or amniotic fluid embolism have been reported.

Treatment: When signs or symptoms of overdosage occur during continuous i.v. administration of Syntocinon, the infusion must be discontinued at once and oxygen should be given to the mother. In cases of water intoxication it is essential to restrict fluid intake, promote diuresis, correct electrolyte imbalance, and control convulsions that may eventually occur. In the case of coma, a free airway should be maintained with routine measures normally employed in the nursing of the unconscious patient.

5. PHARMACOLOGICAL PROPERTIES

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Distribution
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Elimination
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6.3 Shelf life

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6.4 Special precautions for storage

Store between 2°C and 8°C. May be stored up to 30°C for 3 months, but must then be discarded.

6.5 Nature and contents of container

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6.6 Special precautions for disposal and other handling

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(103mmol Na^+ and 51mmol K^+), sodium bicarbonate 1.39%, sodium chloride 0.9%, sodium lactate 1.72%, dextrose 5%, laevulose 20%, macrodex 6%, rheomacrodex 10%, Ringer's solution.

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