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

Summary

EudraCT number	2015-005537-50
Trial protocol	GB
Global end of trial date	31 October 2023

Results information

Result version number	v1 (current)
This version publication date	12 March 2025
First version publication date	12 March 2025

Trial information

Trial identification

Sponsor protocol code	15/BWH/P061

Additional study identifiers

ISRCTN number	ISRCTN99841044
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Funders Reference: HTA 14/140/44, Sponsors Reference: 15/BWH/PO61

Notes:

Sponsors

Sponsor organisation name	Birmingham Women's and Children's NHS FT
Sponsor organisation address	Mindelsohn Way, Birmingham, United Kingdom, B15 2TG
Public contact	Ms Elizabeth Adey, Research and Development, Birmingham Women's and Children's NHS Foundation Trust, e.adey@nhs.net
Scientific contact	Ms Elizabeth Adey, Research and Development, Birmingham Women's and Children's NHS Foundation Trust, e.adey@nhs.net

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 October 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 September 2023
Global end of trial reached?	Yes
Global end of trial date	31 October 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This trial will assess whether high dose regimen oxytocin compared to standard (lower) dose regimen oxytocin will reduce the Caesarean section rate for women with confirmed delay in the first stage of labour,

Protection of trial subjects:

The trial began recruiting on 30th June 2017 and recruitment was suspended for the first time on 17th October 2017 due to two unanticipated issues:
-A site alerted us that clinicians could remove the label from the ampoule thus potentially unblinding the randomised treatment. The manufacturer resolved this by removing the original label and re-labelling the ampoules for the 900 treatment packs still stored with them, but 438 treatment packs had to be destroyed.
-Routine monitoring processes uncovered a total of 233 temperature deviations outside the recommended range of 2-8C across 84% (16/19) of active sites. Extensive revisions to the guidelines for IMP monitoring and storage were introduced, including the use of buffered thermometers. Deviations were reduced to 38 across 29% (7/24) of sites. The buffered thermometers are set up to alarm if the temperature is recorded < 2 or > 30C (where there are no stability data and the ampoules cannot be used). The clinical staff would phone the 24/7 telephone randomisation system to halt recruitment in the site.
This issue was submitted to the MHRA as a Serious Breach which was resolved when we submitted an amendment to restart the trial to HRA and the MHRA on the 20th February 2018. HRA approval was received on 8th June 2018. Local R&D approval was obtained and we re-started recruitment on 27th June 2018.
In August 2018 it was identified that the IMP had been packaged in November 2016 by Sharp Services at ambient temperatures outside those recommended (2-8C), meaning potentially it should have been discarded and not used. The trial was suspended again and the matter was referred to the MHRA. In mid-September 2018, the matter was resolved when the MHRA decided that this process would not have had any detrimental effect on participants. The trial was further delayed due to the covid pandemic, meaning the trial awarded time and funding had been exhausted so we could not re-open.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 120
Worldwide total number of subjects	120
EEA total number of subjects	0

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	120
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

iHOLDs participants were recruited from obstetric departments in 21 participant hospitals across the UK.

Pre-assignment

Screening details:

In the first instance, arrangements were made for all nulliparous women to receive written information about the trial during the antenatal period, ideally at about 34 – 36 weeks. When admitted to the labour ward potential inclusion was then checked by the midwife responsible for her care, with final eligibility determined by an obstetrician.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The drug was prepared for trial use by Sharp Clinical Services, who blinded, labelled, packaged and distributed the treatment packs in temperatures compliant with the
SPC (between 2-8C). Ampoules are only manufactured in 5 and 10iu and treatment packs contain 2 ampoules and will be stored in a fridge on Delivery Suite.

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard Dose Regimen

Arm description:

A standard dose of oxytocin starting at 2mu / min and increasing every 30 minutes up to a maximum of 32 mu / min.

Arm type	Active comparator
Investigational medicinal product name	Oxytocin - Standard Regimen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Standard Strength Oxytocin Solution (10IU in 50mls) Regimen
Time (Mins) - mu/min
0 min - 2 mu/min
30 mins - 4 mu/min
60 mins - 8 mu/min
90 mins - 12 mu/min
120 mins - 16 mu/min
150 mins - 20 mu/min
180 mins - 24 mu/min
210 mins - 28 mu/min
240 mins - 32 mu/min

Arm title	High Dose Regimen

Arm description:

High dose regimen of oxytocin starting at 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

Arm type	Experimental

Investigational medicinal product name	Oxytocin - High Regimen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Higher Strength Oxytocin Solution (20IU in 50mls) Regimen
Time (Mins) - mu/min
0 min - 4 mu/min
30 mins - 8 mu/min
60 mins - 16 mu/min
90 mins - 24 mu/min
120 mins - 32 mu/min
150 mins - 40 mu/min
180 mins - 48 mu/min
210 mins - 56 mu/min
240 mins - 64 mu/min

Number of subjects in period 1[1]	Standard Dose Regimen	High Dose Regimen
Started	58	60
Completed	58	60

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Two participants at one centre have been excluded from analysis for the context of this report due to issues during randomisation and during data collection, one ppt did not give consent and a second was randomised twice and it was unknown which treatment she received.

Period 2

Period 2 title	Primary Outcome (Birth)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard Dose Regimen

Arm description:

A standard dose of oxytocin starting at 2mu / min and increasing every 30 minutes up to a maximum of 32 mu / min.

Arm type	Active comparator
Investigational medicinal product name	Oxytocin - Standard Regimen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Standard Strength Oxytocin Solution (10IU in 50mls) Regimen
Time (Mins) - mu/min
0 min - 2 mu/min

30 mins - 4 mu/min
60 mins - 8 mu/min
90 mins - 12 mu/min
120 mins - 16 mu/min
150 mins - 20 mu/min
180 mins - 24 mu/min
210 mins - 28 mu/min
240 mins - 32 mu/min

Arm title	High Dose Regimen

Arm description:

High dose regimen of oxytocin starting at 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

Arm type	Experimental
Investigational medicinal product name	Oxytocin - High Regimen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Higher Strength Oxytocin Solution (20IU in 50mls) Regimen
Time (Mins) - mu/min
0 min - 4 mu/min
30 mins - 8 mu/min
60 mins - 16 mu/min
90 mins - 24 mu/min
120 mins - 32 mu/min
150 mins - 40 mu/min
180 mins - 48 mu/min
210 mins - 56 mu/min
240 mins - 64 mu/min

Number of subjects in period 2	Standard Dose Regimen	High Dose Regimen
Started	58	60
Completed	58	60

Baseline characteristics

Reporting groups	
Reporting group title	Standard Dose Regimen
Reporting group description:	
A standard dose of oxytocin starting at 2mu / min and increasing every 30 minutes up to a maximum of 32 mu / min.	
Reporting group title	High Dose Regimen
Reporting group description:	
High dose regimen of oxytocin starting at 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	

Reporting group values	Standard Dose Regimen	High Dose Regimen	Total
Number of subjects	58	60	118
Age categorical Units: Subjects			
<20	4	5	9
20 to <30	27	29	56
30 to < 40	27	26	53
40 and over	0	0	0
Age continuous Units: years			
arithmetic mean	28.7	28.7	
standard deviation	± 5.6	± 5.4	-
Gender categorical Units: Subjects			
Female	58	60	118
Male	0	0	0
Ethnicity Units: Subjects			
UK (White)	46	46	92
South Asian (Asian)	4	3	7
Southern & Other European (White)	3	4	7
Northern European (White)	2	2	4
South East Asian (White)	0	3	3
African or African-Caribbean (Black)	1	1	2
Other Non-European (Other)	0	1	1
Don't Know / NA	2	0	2
Degree of Cervical Dilation (cm) Units: Subjects			
<6cm	28	28	56
>=6cm	30	32	62
BMI Units: kilogram(s)/square metre			
arithmetic mean	24.7	25.6	
standard deviation	± 4.7	± 5.2	-
Gestational Age at Randomisation (weeks)			

Units: Weeks			
median	39.57	39.43	
inter-quartile range (Q1-Q3)	39.14 to 40.14	38.86 to 40.14	-

End points

End points reporting groups

Reporting group title	Standard Dose Regimen
Reporting group description:	
A standard dose of oxytocin starting at 2mu / min and increasing every 30 minutes up to a maximum of 32 mu / min.	
Reporting group title	High Dose Regimen
Reporting group description:	
High dose regimen of oxytocin starting at 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	
Reporting group title	Standard Dose Regimen
Reporting group description:	
A standard dose of oxytocin starting at 2mu / min and increasing every 30 minutes up to a maximum of 32 mu / min.	
Reporting group title	High Dose Regimen
Reporting group description:	
High dose regimen of oxytocin starting at 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	

Primary: Mode of Delivery of Birth

End point title	Mode of Delivery of Birth[1]
End point description:	
The primary outcome was the effect on caesarean section rate of high does regimen versus standard dose regimen oxytocin. We also looked at what the mode of delivery was if not a CS.	
End point type	Primary
End point timeframe:	
Collected at time of birth	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal analyses was done for the trial due to low numbers given the trial closed early.

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: women				
Caesarean Section	20	16		
Spontaneous Vaginal Birth	18	20		
Instrumental	20	24		

Statistical analyses

No statistical analyses for this end point

Secondary: Category of Emergency

End point title	Category of Emergency

End point description:

End point type	Secondary

End point timeframe:

Measured at birth in women who had a caesarean section

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	16		
Units: Women				
Category 1: Immediate threat to life	6	5		
Category 2: Maternal or fetal compromise	11	11		
Category 3: Early birth needed but no compromise	3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Reason for Caesarean Section

End point title	Reason for Caesarean Section

End point description:

End point type	Secondary

End point timeframe:

Measured at time of birth in women who had a caesarean.

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[2]	16[3]		
Units: Women				
Delay in 1st stage	13	11		
Delay in 2nd stage	20	2		
Maternal Request	1	0		
Hyperstimulation	1	1		
CTG concerns without FBS	16	14		
Abnormal FBS	0	1		

Failed Instrumental	5	0		
Unsuitable for instrumental	10	10		
Other	3	2		

Notes:

[2] - More than one reason can be selected

[3] - More than 1 reason can be selected

Statistical analyses

No statistical analyses for this end point

Secondary: Epidural Use during Labour

End point title	Epidural Use during Labour

End point description:

End point type	Secondary

End point timeframe:

Collected throughout birth

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: women				
Yes	47	46		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of first stage of labour

End point title	Duration of first stage of labour

End point description:

End point type	Secondary

End point timeframe:

During labour

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	42		
Units: minute				
arithmetic mean (standard deviation)	818 (± 221)	888 (± 249)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of second stage of labour

End point title	Duration of second stage of labour

End point description:

End point type	Secondary

End point timeframe:

During labour

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: minute				
arithmetic mean (standard deviation)	144 (± 64)	150 (± 77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of third stage of labour

End point title	Duration of third stage of labour

End point description:

End point type	Secondary

End point timeframe:

During Labour

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: minute				
arithmetic mean (standard deviation)	8 (± 16)	8 (± 7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time from randomisation to Birth

End point title	Time from randomisation to Birth

End point description:

End point type	Secondary

End point timeframe:

Measured at Birth

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	60		
Units: minute				
median (inter-quartile range (Q1-Q3))	431 (349 to 548)	368 (242 to 608)		

Statistical analyses

No statistical analyses for this end point

Secondary: Degree of perineal trauma

End point title	Degree of perineal trauma

End point description:

End point type	Secondary

End point timeframe:

During labour

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: women				
None (intact perineum)	14	20		
First Degree	2	3		
Second Degree	17	16		
Third Degree	2	1		
Fourth Degree	0	1		
Missing	3	3		
NA (CS)	20	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Fetal blood sampling during labour or significant STAN event

End point title	Fetal blood sampling during labour or significant STAN event

End point description:

End point type	Secondary

End point timeframe:

During labour

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: women	9	12		

Statistical analyses

No statistical analyses for this end point

Secondary: Abnormal cardiogram leading to immediate birth without FBS

End point title	Abnormal cardiogram leading to immediate birth without FBS

End point description:

End point type	Secondary

End point timeframe:

During labour

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: women	13	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Women with blood loss > 500ml (PPH)

End point title	Women with blood loss > 500ml (PPH)

End point description:

End point type	Secondary

End point timeframe:

During labour

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: women	27	25		

Statistical analyses

No statistical analyses for this end point

Secondary: IV Antibiotics for suspected or confirmed chorioamnionitis

End point title	IV Antibiotics for suspected or confirmed chorioamnionitis

End point description:

End point type	Secondary

End point timeframe:

Until discharge

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: women	3	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Active management of third stage of labour

End point title	Active management of third stage of labour

End point description:

End point type	Secondary

End point timeframe:

During labour

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: women	55	55		

Statistical analyses

No statistical analyses for this end point

Secondary: Length of stay after birth in hospital

End point title	Length of stay after birth in hospital

End point description:

End point type	Secondary

End point timeframe:

From birth until discharge

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: day				
median (inter-quartile range (Q1-Q3))	1.5 (1 to 3)	1 (1 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rotation Required

End point title	Rotation Required
End point description: For instrumental births	
End point type	Secondary
End point timeframe: During labour	

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: women	7	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Ventouse

End point title	Ventouse
End point description: In instrumental births	
End point type	Secondary
End point timeframe: During labour	

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[4]	24[5]		
Units: women				
No	19	20		
Successful	3	2		
Failed	1	2		

Notes:

[4] - Only women with successful or failed instrumental birth

[5] - Only women with successful or failed instrumental birth

Statistical analyses

No statistical analyses for this end point

Secondary: Forceps

End point title	Forceps
End point description:	
In instrumental births	
End point type	Secondary
End point timeframe:	
During labour	

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[6]	24[7]		
Units: women				
No	4	2		
Successful	15	22		
Failed	3	0		

Notes:

[6] - Only women with successful or failed instrumental birth

[7] - Only women with successful or failed instrumental birth

Statistical analyses

No statistical analyses for this end point

Secondary: Primary reason for Instrumental Birth

End point title	Primary reason for Instrumental Birth
End point description:	
In instrumental birth	
End point type	Secondary
End point timeframe:	
At birth	

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[8]	24[9]		
Units: women				
CTG Concerns without resort to FBS	18	12		
Abnormal FBS (<= 7.20)	0	1		
Delay in 2nd stage	14	15		
Pushing challenges	2	1		
Other	1	2		

Notes:

[8] - Only women with successful or failed instrumental birth. Can select more than 1 reason.

[9] - Only women with successful or failed instrumental birth. Can select more than 1 reason.

Statistical analyses

No statistical analyses for this end point

Secondary: Neonatal: Gender

End point title	Neonatal: Gender
End point description: Measured in babies	
End point type	Secondary
End point timeframe: At birth	

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: babies				
Female	31	29		
Male	27	31		

Statistical analyses

No statistical analyses for this end point

Secondary: Neonatal: Birthweight

End point title	Neonatal: Birthweight
End point description: Neonatal outcome	
End point type	Secondary

End point timeframe:
At birth

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: kilogram(s)				
arithmetic mean (standard deviation)	3.52 (± 0.44)	3.51 (± 0.42)		

Statistical analyses

No statistical analyses for this end point

Secondary: Apgar score at 5 minutes

End point title	Apgar score at 5 minutes

End point description:

End point type	Secondary

End point timeframe:
At birth

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: score				
median (inter-quartile range (Q1-Q3))	10 (9 to 10)	9.5 (9 to 10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Arterial cord blood gases when collected

End point title	Arterial cord blood gases when collected

End point description:

End point type	Secondary

End point timeframe:
At birth

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: pH				
arithmetic mean (standard deviation)	7.22 (± 0.1)	7.22 (± 0.09)		

Statistical analyses

No statistical analyses for this end point

Secondary: Venous cord blood gases when collected

End point title	Venous cord blood gases when collected

End point description:

End point type	Secondary

End point timeframe:

At Birth

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	39		
Units: pH				
arithmetic mean (standard deviation)	7.27 (± 0.09)	7.29 (± 0.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Breastfeeding rates on discharge from hospital

End point title	Breastfeeding rates on discharge from hospital

End point description:

End point type	Secondary

End point timeframe:

At discharge

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: Babies	42	50		

Statistical analyses

No statistical analyses for this end point

Secondary: Discharge home with mother

End point title	Discharge home with mother

End point description:

End point type	Secondary

End point timeframe:

At discharge

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: Babies	58	60		

Statistical analyses

No statistical analyses for this end point

Secondary: Resuscitation

End point title	Resuscitation

End point description:

End point type	Secondary

End point timeframe:

At birth

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: Babies	8	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Reason for neonatal review on ward

End point title	Reason for neonatal review on ward
End point description:	
Excluding routine baby check	
End point type	Secondary
End point timeframe:	
From birth to discharge	

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: babies				
Infection	13	6		
Other	5	7		
Baby not reviewed	36	45		

Statistical analyses

No statistical analyses for this end point

Secondary: Admitted to NNU

End point title	Admitted to NNU
End point description:	
End point type	Secondary
End point timeframe:	
From birth to discharge	

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: babies	3	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Level of NNU Care received

End point title	Level of NNU Care received

End point description:

End point type	Secondary

End point timeframe:

from birth to discharge

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	3		
Units: babies				
Transitional	2	1		
Special Care (Level 1)	0	1		
HDC (Level 2)	1	0		
Intensive Care (Level 3)	0	0		
Missing	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Maternal: Headache

End point title	Maternal: Headache

End point description:

End point type	Secondary

End point timeframe:

From birth to discharge

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: women	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Maternal: Nausea

End point title	Maternal: Nausea

End point description:

End point type	Secondary

End point timeframe:
from birth to discharge

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: women	7	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Maternal: Vomiting

End point title	Maternal: Vomiting

End point description:

End point type	Secondary

End point timeframe:
from birth to discharge

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: women	5	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Maternal: Tachycardia/Bradycardia

End point title	Maternal: Tachycardia/Bradycardia

End point description:

End point type	Secondary

End point timeframe:

from birth to discharge

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: women	12	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Maternal: Uterine Tachysystole

End point title	Maternal: Uterine Tachysystole

End point description:

End point type	Secondary

End point timeframe:

During birth

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: women	18	24		

Statistical analyses

No statistical analyses for this end point

Secondary: Maternal: Uterine Hyperstimulation

End point title	Maternal: Uterine Hyperstimulation

End point description:

End point type	Secondary

End point timeframe:

during birth

End point values	Standard Dose Regimen	High Dose Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: women	14	16		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Assessment type	Non-systematic

Dictionary used

Dictionary name	Trial Specific
Dictionary version	1.0

Reporting groups

Reporting group title	Standard Dose Regimen

Reporting group description:

A standard dose of oxytocin starting at 2mu / min and increasing every 30 minutes up to a maximum of 32 mu / min.

Reporting group title	High Dose Regimen

Reporting group description:

High dose regimen of oxytocin starting at 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

Serious adverse events	Standard Dose Regimen	High Dose Regimen	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 58 (25.86%)	7 / 60 (11.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Intensive care - Mother	Additional description: Admission to HDU/ITU		
subjects affected / exposed	2 / 58 (3.45%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intensive care - Neonatal	Additional description: Neonatal intensive care		
subjects affected / exposed	0 / 58 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Postpartum haemorrhage	Additional description: Triggering massive obstetric haemorrhage		
subjects affected / exposed	3 / 58 (5.17%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
Jaundice neonatal			
subjects affected / exposed	1 / 58 (1.72%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis neonatal	Additional description: Suspected sepsis		
subjects affected / exposed	6 / 58 (10.34%)	2 / 60 (3.33%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Standard Dose Regimen	High Dose Regimen	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 58 (44.83%)	30 / 60 (50.00%)	
Pregnancy, puerperium and perinatal conditions			
Uterine hyperstimulation			
subjects affected / exposed	14 / 58 (24.14%)	16 / 60 (26.67%)	
occurrences (all)	14	16	
Uterine tachysystole			
subjects affected / exposed	18 / 58 (31.03%)	24 / 60 (40.00%)	
occurrences (all)	18	24	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 August 2016	Made in response to review by the MHRA: o Changes to the description of the monitoring in labour that is undertaken to both mother and baby o Clarity of the descriptions for adverse drug reactions and events and reporting arrangements Other: • 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

15 April 2021	• Trial logo replaced • Minor amendments and correction of minor mistakes found within the protocol Contacts and Roles: Contacts updated, including the removal of contact details for committee members Background: Updated with data from a published trial Trial Aim and Objectives: Updated to include summary of pilot study Trial Design: Changes to eligibility criteria Treatment Allocation: • Instructions added for daily IMP temperature logging and reporting • Addition of the following sections: Drug interaction or contraindications, treatment modification, cessation of treatment/continuation after the trial • Withdrawal of trial/treatment and change of status within the trial section replaced Adverse Event Reporting: Restructuring of section and addition of new information and instructions for SAE reporting Data Management: • Addition of case report form schedule and summary of data collection points, personnel and training requirements • Removal of duplicated section (long term storage of data) Statistical Methods and analysis: • Additions to description of statistical analysis outline plan • Amendments to primary outcome analysis and subgroup analysis sections Data Access and Quality Assurance: Addition of ethical considerations section Organisation and Responsibilities: Update to centre eligibility rules, PI and Research Midwife responsibilities Regulatory and Ethical Approval: Amendments to funding and cost implications section regarding financial support for sites Reporting, Publications and Notification of results: Replaced text for authorship and publication policy

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

17 October 2017	A site alerted us that clinicians could remove the label from the ampoule thus potentially unblinding the randomised treatment. The manufacturer resolved this by removing the original label and re-labelling the ampoules for the 900 treatment packs still stored with them, but 438 treatment packs had to be destroyed. Routine monitoring processes uncovered a total of 233 temperature deviations outside the recommended range of 2-8oC across 84% (16/19) of active sites. Extensive revisions to the guidelines for Investigational Medicinal Product (IMP) monitoring and storage were introduced, including the use of buffered thermometers. Deviations were reduced to 38 across 29% (7/24) of sites. The buffered thermometers are set up to alarm if the temperature is recorded < 2oC or > 30oC (where there are no stability data and the ampoules cannot be used). The clinical staff would phone the 24/7 telephone randomisation system to halt recruitment in the site. This issue was submitted to the MHRA as a Serious Breach which was resolved when we submitted an amendment to restart the trial to Health Research Authority (HRA) and the MHRA on the 20th February 2018. HRA approval was received on 8th June 2018. Local Research & Development (R&D) approval was obtained and we re-started recruitment on 27th June 2018.	27 June 2018
01 August 2018	In August 2018 it was identified that the IMP had been packaged in November 2016 by Sharp Services at ambient temperatures outside those recommended (2-8oC), meaning potentially it should have been discarded and not used. The trial was suspended again and the matter was referred to the MHRA. In mid-September2018, the matter was resolved when the MHRA decided that this process would not have had any detrimental effect on participants. However, the trial awarded time and funding had been exhausted so we could not re-open. Further funding was identified in October 2020 for HOLDS and the intention was to run HOLDS concurrently with iHOLDS (HTA 17/137/02). Funding started in October 2019, with recruitment due to begin in July 2020 which was then delayed by the impact of the COVID-19 pandemic. We restarted recruitment to the trial in June 2022.	01 June 2022

Notes:

Limitations and caveats

None reported