Clinical trial results:
Intramuscular oxytocics: A multi-centre randomised comparison study of intramuscular Carbetocin, Syntocinon and Syntometrine for the third stage of labour following vaginal birth

Summary

EudraCT number	2014-001948-37
Trial protocol	GB
Global end of trial date	24 July 2018

Results information

Result version number	v1 (current)
This version publication date	15 February 2020
First version publication date	15 February 2020

Trial information

Trial identification

Sponsor protocol code	3344

Additional study identifiers

ISRCTN number	ISRCTN10232550
ClinicalTrials.gov id (NCT number)	NCT02216383
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	North Bristol NHS Trust
Sponsor organisation address	Southmead Hospital, Bristol, United Kingdom, BS10 5NB
Public contact	Helen Lewis-White, North Bristol NHS Trust, 0117 41 49333, Helen.Lewis-White@nbt.nhs.uk
Scientific contact	Prof Tim Draycott, North Bristol NHS Trust, 0117 41 46764, tim.draycott@nbt.nhs.uk

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	12 August 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Is Carbetocin as least as effective as Syntometrine, and more effective than Syntocinon, at preventing post partum haemorrhage after vaginal birth?

Protection of trial subjects:

Labouring women are a vulnerable population. Plans for recruitment were developed in line with Royal College of Obstetrician and Gynaecologist Clinical Governance Advice 6a (August 2010): "Obtaining valid consent to
participate in research while in labour".
To try and ensure that patients had as much time as possible to consider the study and whether they would like to
participate, information was given to patients antenatally at ~20 weeks gestation when they attended antenatal clinic
for their routine anomaly scan.
If a woman was invited to take part a sticker was placed in the front of the notes. This sticker helped avoid situations in which patients who did not want to participate were not repeatedly asked.
In labour, midwives were an advocate for the patient and acted as their "gatekeeper", having established the patient's birth preferences.
Exclusion criteria was in place (e.g. stillbirth, prisoners, women aged under 18years, those unable to read and comprehend the study) to ensure that the most vulnerable were not recruited as it was felt not appropriate.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2014
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: 5717
Worldwide total number of subjects	5717
EEA total number of subjects	5717

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)	5717
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Opportunistically invited women from 20 weeks gestation onwards. This was "opportunistic", as it mainly involved women who happened to attend the hospital antenatal ward, antenatal clinic, and Maternity Assessment Unit in their last few weeks of pregnancy.

Pre-assignment

Screening details:

Screening was completed by a research midwife. Inclusion criteria; <18 years old at the time of birth, Vaginal birth (spontaneous/instrumental), singleton pregnancy, any gestation.

Period 1

Period 1 title	Overall Trial Period (All trial) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Carbetocin

Arm description:

This group were randomised to receive Carbetocin

Arm type	Active comparator
Investigational medicinal product name	Carbetocin
Investigational medicinal product code	ATC H01BB03 PR1
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

100µg given once. Formula; (2S)1[(3S,6S,9S,12S,15S)12[(2S)butan2yl]9(2carbamoylethyl)6(carbamoylmethyl)15[(4hydroxyphenyl)methyl]16methyl5,8,11,14,17pentaoxo1thia4,7,10,13,16pentazacycloicosane3carbonyl]N[(1S)1(carbamoylmethylcarbamoyl)3methylbutyl]pyrrolidine2carboxamide

Arm title	Syntocinon

Arm description:

The group was randomised to receive Syntocinon

Arm type	Active comparator
Investigational medicinal product name	Syntocinon
Investigational medicinal product code	ATC H01BB02 PR2
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intramuscular use

Dosage and administration details:

10iU. Given once.

Arm title	Syntometrine

Arm description:

The group was randomised to receive Syntometrine

Arm type	Active comparator

Investigational medicinal product name	Syntometrine
Investigational medicinal product code	ATC G02AC PR3
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

5iU given once. Formula; c19h23n3o2

Number of subjects in period 1	Carbetocin	Syntocinon	Syntometrine
Started	1909	1896	1912
Completed	1909	1896	1912

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial Period (All trial)

Reporting group description: -

Reporting group values	Overall Trial Period (All trial)	Total	
Number of subjects	5717	5717	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	5717	5717	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	5717	5717	
Male	0	0	

End points

End points reporting groups

Reporting group title	Carbetocin
Reporting group description:	
This group were randomised to receive Carbetocin	
Reporting group title	Syntocinon
Reporting group description:	
The group was randomised to receive Syntocinon	
Reporting group title	Syntometrine
Reporting group description:	
The group was randomised to receive Syntometrine	
Subject analysis set title	PP Population - Carbetocin
Subject analysis set type	Per protocol
Subject analysis set description:	
In supplementary analyses we report results per protocol (PP; i.e. participants who were randomised, remained eligible, received uterotonic which first randomised to, analysed according to uterotonic received).	
Subject analysis set title	PP Population - Syntocinon
Subject analysis set type	Per protocol
Subject analysis set description:	
In supplementary analyses we report results per protocol (PP; i.e. participants who were randomised, remained eligible, received uterotonic which first randomised to, analysed according to uterotonic received).	
Subject analysis set title	PP Population - Syntometrine
Subject analysis set type	Per protocol
Subject analysis set description:	
In supplementary analyses we report results per protocol (PP; i.e. participants who were randomised, remained eligible, received uterotonic which first randomised to, analysed according to uterotonic received).	

Primary: Requirement for additional uterotonic drug - (mITT population)

End point title	Requirement for additional uterotonic drug - (mITT population)
End point description:	
End point type	Primary
End point timeframe:	
From the IMP administration to discharge	

End point values	Carbetocin	Syntocinon	Syntometrine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1909	1896	1912	
Units: Number	1909	1896	1912	

Attachments (see zip file)	Logistic Regression/Table 4 - logistic regression_v4.docx

Statistical analyses

Statistical analysis title	Syntometrine v Carbetocin

Statistical analysis description:

The primary outcome variable is the need for additional uterotonic drugs. An omnibus test for differences in the proportions needing (not needing) additional uterotonic drugs with be examined using the chi-square test of association.

Comparison groups	Carbetocin v Syntometrine
Number of subjects included in analysis	3821
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.004
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	0.93

Notes:

[1] - o Superiority comparison between Syntometrine and Syntocinon
o Superiority comparison between Carbetocin and Syntocinon
o Non-inferiority comparison between Carbetocin and Syntometrine

Statistical analysis title	Syntometrine v Syntocinon

Statistical analysis description:

The primary outcome variable is the need for additional uterotonic drugs. An omnibus test for differences in the proportions needing (not needing) additional uterotonic drugs with be examined using the chi-square test of association.

Comparison groups	Syntocinon v Syntometrine
Number of subjects included in analysis	3808
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.002
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	0.91

Notes:

[2] - o Superiority comparison between Syntometrine and Syntocinon
o Superiority comparison between Carbetocin and Syntocinon
o Non-inferiority comparison between Carbetocin and Syntometrine

Statistical analysis title	Syntocinon v Carbetocin

Statistical analysis description:

The primary outcome variable is the need for additional uterotonic drugs. An omnibus test for differences in the proportions needing (not needing) additional uterotonic drugs with be examined using the chi-square test of association.

Comparison groups	Carbetocin v Syntocinon

Number of subjects included in analysis	3805
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.78
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.2

Notes:

[3] - o Superiority comparison between Syntometrine and Syntocinon
o Superiority comparison between Carbetocin and Syntocinon
o Non-inferiority comparison between Carbetocin and Syntometrine

Primary: Requirement for additional uterotonic drug - (PP population)

End point title	Requirement for additional uterotonic drug - (PP population)

End point description:

End point type	Primary

End point timeframe:

From the IMP administration to discharge

End point values	PP Population - Carbetocin	PP Population - Syntocinon	PP Population - Syntometrine	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1885	1869	1912	
Units: Number	359	359	293	

Statistical analyses

Statistical analysis title	Syntometrine v Carbetocin
Comparison groups	PP Population - Carbetocin v PP Population - Syntometrine
Number of subjects included in analysis	3797
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.004
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	0.93

Statistical analysis title	Syntometrine v Syntocinon
Comparison groups	PP Population - Syntocinon v PP Population - Syntometrine
Number of subjects included in analysis	3781
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	0.92

Statistical analysis title	Oxytocin v Carbetocin
Comparison groups	PP Population - Syntocinon v PP Population - Carbetocin
Number of subjects included in analysis	3754
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.89
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.19

Secondary: Median Blood Loss (ml)	
End point title	Median Blood Loss (ml)
End point description:	

End point type	Secondary
End point timeframe:	
Administration of IMP until discharge	

End point values	Carbetocin	Syntocinon	Syntometrine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1909	1896	1912	
Units: milliequivalent(s)/millilitre				
number (not applicable)	500	500	483	

Statistical analyses

No statistical analyses for this end point

Secondary: Estimated Blood Loss ≥500ml

End point title	Estimated Blood Loss ≥500ml

End point description:

End point type	Secondary

End point timeframe:

IMP administration to discharge

End point values	Carbetocin	Syntocinon	Syntometrine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1909	1896	1912	
Units: millicurie(s)/millilitre				
number (not applicable)	961	949	483	

Attachments (see zip file)	Logistic Regression/Table 4 - logistic regression_v4.docx

Statistical analyses

Statistical analysis title	Syntometrine v Carbetocin
Comparison groups	Carbetocin v Syntometrine
Number of subjects included in analysis	3821
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.16
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.04

Statistical analysis title	Syntometrine v Syntocinon
Comparison groups	Syntometrine v Syntocinon
Number of subjects included in analysis	3808
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.05

Statistical analysis title	Syntocinon v Carbetocin
Comparison groups	Carbetocin v Syntocinon
Number of subjects included in analysis	3805
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.12

Secondary: Estimated Blood Loss ≥ 1000ml	
End point title	Estimated Blood Loss ≥ 1000ml
End point description:	

End point type	Secondary
End point timeframe:	
Administration of IMP until discharge	

End point values	Carbetocin	Syntocinon	Syntometrine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1909	1896	1912	
Units: millicurie(s)/millilitre				
number (not applicable)	330	355	352	

Statistical analyses

Statistical analysis title	Syntometrine v Carbetocin
Comparison groups	Carbetocin v Syntometrine
Number of subjects included in analysis	3821
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.37
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.27

Statistical analysis title	Syntometrine v Synocinon
Comparison groups	Syntometrine v Syntocinon
Number of subjects included in analysis	3808
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.82
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.16

Statistical analysis title	Syntocinon v Carbetocin
Comparison groups	Carbetocin v Syntocinon

Number of subjects included in analysis	3805
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.26
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.3

Secondary: Estimated Blood Loss ≥ 2000ml

End point title	Estimated Blood Loss ≥ 2000ml
End point description:	

End point type	Secondary
End point timeframe:	
Administration of IMP until discharge	

End point values	Carbetocin	Syntocinon	Syntometrine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1909	1896	1912	
Units: millicurie(s)/millilitre				
number (not applicable)	56	74	59	

Statistical analyses

Statistical analysis title	Syntometrine v Carbetocin
Comparison groups	Syntometrine v Carbetocin
Number of subjects included in analysis	3821
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.79
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.53

Statistical analysis title	Syntometrine v Syntocinon
Comparison groups	Syntometrine v Syntocinon
Number of subjects included in analysis	3808
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.11

Statistical analysis title	Syntocinon v Carbetocin
Comparison groups	Carbetocin v Syntocinon
Number of subjects included in analysis	3805
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.9

Secondary: Blood Transfusion	
End point title	Blood Transfusion
End point description:	

End point type	Secondary
End point timeframe:	
IMP administration until discharge	

End point values	Carbetocin	Syntocinon	Syntometrine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1909	1896	1912	
Units: Adverse Events	54	58	51	

Statistical analyses

Statistical analysis title	Syntometrine v Carbetocin
Comparison groups	Syntometrine v Carbetocin
Number of subjects included in analysis	3821
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.09
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.34

Statistical analysis title	Syntometrine v Syntocinon
Comparison groups	Syntocinon v Syntometrine
Number of subjects included in analysis	3808
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.52
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.27

Statistical analysis title	Syntocinon v Carbetocin
Comparison groups	Carbetocin v Syntocinon

Number of subjects included in analysis	3805
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.68
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.58

Secondary: Manual removal of placenta

End point title	Manual removal of placenta
End point description:	

End point type	Secondary
End point timeframe:	
Administration of IMP until discharge	

End point values	Carbetocin	Syntocinon	Syntometrine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1909	1896	1912	
Units: Yes/No	57	43	49	

Statistical analyses

Statistical analysis title	Syntometrine v Carbetocin
Comparison groups	Syntometrine v Carbetocin
Number of subjects included in analysis	3821
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.63
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.26

Statistical analysis title	Syntometrine v Syntocinon
Comparison groups	Syntometrine v Syntocinon
Number of subjects included in analysis	3808
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.72

Statistical analysis title	Syntocinon v Carbetocin
Comparison groups	Syntocinon v Carbetocin
Number of subjects included in analysis	3805
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.13

Secondary: Other Surgical/mechanical methods to treat PPH	
End point title	Other Surgical/mechanical methods to treat PPH
End point description:	

End point type	Secondary
End point timeframe:	
Administration of IMP until discharge	

End point values	Carbetocin	Syntocinon	Syntometrine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1909	1896	1912	
Units: Number of Incidence	42	58	38	

Statistical analyses

Statistical analysis title	Syntometrine v Carbetocin
Comparison groups	Carbetocin v Syntometrine
Number of subjects included in analysis	3821
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.64
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.4

Statistical analysis title	Syntometrine v Syntocinon
Comparison groups	Syntometrine v Syntocinon
Number of subjects included in analysis	3808
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.97

Statistical analysis title	Syntocinon v Carbetocin
Comparison groups	Carbetocin v Syntocinon

Number of subjects included in analysis	3805
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	2.1

Secondary: Hypertension in first two postnatal hours	
End point title	Hypertension in first two postnatal hours
End point description: Defined as SBP ≥140mmHg or DBP ≥90mmHg in the first two postnatal hours	
End point type	Secondary
End point timeframe: Administration of the IMP until two hours postnatal	

End point values	Carbetocin	Syntocinon	Syntometrine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1909	1896	1912	
Units: number of incidence	132	134	233	

Statistical analyses

Statistical analysis title	Syntometrine v Carbetocin
Comparison groups	Carbetocin v Syntometrine
Number of subjects included in analysis	3821
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.51
upper limit	2.37

Statistical analysis title	Syntometrine v Syntocinon
Comparison groups	Syntometrine v Syntocinon
Number of subjects included in analysis	3808
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.48
upper limit	2.32

Statistical analysis title	Syntocinon v Carbetocin
Comparison groups	Carbetocin v Syntocinon
Number of subjects included in analysis	3805
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.88
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.31

Secondary: Hypotension in first two postnatal hours	
End point title	Hypotension in first two postnatal hours
End point description: Defined as DBP <90mmHg in the first two postnatal hours	
End point type	Secondary
End point timeframe: Administration of the IMP until2 hours postnatal	

End point values	Carbetocin	Syntocinon	Syntometrine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1909	1896	1912	
Units: number of incidence	31	47	30	

Statistical analyses

Statistical analysis title	Syntometrine v Carbetocin
Comparison groups	Carbetocin v Syntometrine
Number of subjects included in analysis	3821
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.91
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.7

Statistical analysis title	Syntometrine v Syntocinon
Comparison groups	Syntocinon v Syntometrine
Number of subjects included in analysis	3808
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.83
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.06

Statistical analysis title	Syntocinon v Carbetocin
Comparison groups	Carbetocin v Syntocinon

Number of subjects included in analysis	3805
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	2.43

Secondary: Nausea

End point title	Nausea
End point description:	

End point type	Secondary
End point timeframe:	
Administration of the IMP until 14 day follow up	

End point values	Carbetocin	Syntocinon	Syntometrine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1909	1896	1912	
Units: number of incidence	153	169	458	

Statistical analyses

Statistical analysis title	Syntometrine v Carbetocin
Comparison groups	Carbetocin v Syntometrine
Number of subjects included in analysis	3821
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.98
upper limit	4.4

Statistical analysis title	Syntometrine v Syntocinon
Comparison groups	Syntocinon v Syntometrine
Number of subjects included in analysis	3808
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.67
upper limit	3.9

Statistical analysis title	Syntocinon v Carbetocin
Comparison groups	Carbetocin v Syntocinon
Number of subjects included in analysis	3805
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.41

Secondary: Vomiting	
End point title	Vomiting
End point description: Vomiting in those not already vomiting in labour	
End point type	Secondary
End point timeframe: Administration of IMP until 14 day follow up	

End point values	Carbetocin	Syntocinon	Syntometrine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1909	1896	1912	
Units: number of incidence	91	92	337	

Statistical analyses

Statistical analysis title	Syntometrine v Carbetocin
Comparison groups	Carbetocin v Syntometrine
Number of subjects included in analysis	3821
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	4.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.36
upper limit	5.45

Statistical analysis title	Syntometrine v Syntocinon
Comparison groups	Syntocinon v Syntometrine
Number of subjects included in analysis	3808
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.3
upper limit	5.35

Statistical analysis title	Syntocinon v Carbetocin
Comparison groups	Carbetocin v Syntocinon

Number of subjects included in analysis	3805
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.91
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.37

Secondary: Headache

End point title	Headache

End point description:

End point type	Secondary

End point timeframe:

Administration of the IMP to 14 days follow up

End point values	Carbetocin	Syntocinon	Syntometrine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1909	1896	1912	
Units: number of incidence	28	26	65	

Statistical analyses

Statistical analysis title	Syntometrine v Carbetocin
Comparison groups	Syntocinon v Carbetocin
Number of subjects included in analysis	3805
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.51
upper limit	3.7

Statistical analysis title	Syntometrine v Syntocinon
Comparison groups	Syntocinon v Syntometrine
Number of subjects included in analysis	3808
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.6
upper limit	4.02

Statistical analysis title	Synotcinon v Carbetocin
Comparison groups	Syntocinon v Carbetocin
Number of subjects included in analysis	3805
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.6

Secondary: Dizziness	
End point title	Dizziness
End point description:	

End point type	Secondary
End point timeframe:	
Administration of the IMP until 14 day follow up	

End point values	Carbetocin	Syntocinon	Syntometrine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1909	1896	1912	
Units: number of incidence	123	163	188	

Statistical analyses

Statistical analysis title	Syntometrine v Carbetocin
Comparison groups	Carbetocin v Syntometrine
Number of subjects included in analysis	3821
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.25
upper limit	2.01

Statistical analysis title	Syntometrine v Syntocinon
Comparison groups	Syntometrine v Syntocinon
Number of subjects included in analysis	3808
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.45

Statistical analysis title	Syntocinon v Carbetocin
Comparison groups	Syntocinon v Carbetocin

Number of subjects included in analysis	3805
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	1.74

Secondary: Abdominal pain

End point title	Abdominal pain

End point description:

End point type	Secondary

End point timeframe:

Administration of the IMP until 14 days follow up

End point values	Carbetocin	Syntocinon	Syntometrine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1909	1896	1912	
Units: number of incidence	99	129	162	

Statistical analyses

Statistical analysis title	Syntometrine v Carbetocin
Comparison groups	Carbetocin v Syntometrine
Number of subjects included in analysis	3821
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.31
upper limit	2.19

Statistical analysis title	Syntometrine v Syntocinon
Comparison groups	Syntometrine v Syntocinon
Number of subjects included in analysis	3808
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.62

Statistical analysis title	Syntocinon v Carbetocin
Comparison groups	Carbetocin v Syntocinon
Number of subjects included in analysis	3805
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	1.75

Secondary: Self-reported ability to bond with/care forbaby infirst two postnatal hours

End point title	Self-reported ability to bond with/care forbaby infirst two postnatal hours

End point description:

End point type	Secondary

End point timeframe:

Administration to the IMP up to two hours postnatal

End point values	Carbetocin	Syntocinon	Syntometrine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1909	1896	1912	
Units: number of incidence	56	83	160	

Statistical analyses

Statistical analysis title	Syntometrine v Carbetocin
Comparison groups	Syntometrine v Carbetocin
Number of subjects included in analysis	3821
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.22
upper limit	4.13

Statistical analysis title	Syntometrine v Syntocinon
Comparison groups	Syntocinon v Syntometrine
Number of subjects included in analysis	3808
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.52
upper limit	2.62

Statistical analysis title	Syntocinon v Carbetocin
Comparison groups	Syntocinon v Carbetocin

Number of subjects included in analysis	3805
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	2.15

Secondary: Mean EQ-5D Utility Score: all returned questionaires

End point title	Mean EQ-5D Utility Score: all returned questionaires
End point description: Standard deviations not given	
End point type	Secondary
End point timeframe: Conducted at recruitment, Day 1 and Day 14	

End point values	Carbetocin	Syntocinon	Syntometrine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1909	1896	1912	
Units: EQ-5D Index Scores				
arithmetic mean (standard deviation)				
Antenatal	0.8115 (± .16954)	0.8107 (± .17524)	0.8104 (± .16954)	
Day One	0.7578 (± .17879)	0.7553 (± 17460)	0.7470 (± .17879)	
Day 14	0.8998 (± .12427)	0.9031 (± .12520)	0.8910 (± .12556)	
Participants with a complete EQ-5D dataset	0.8995 (± 0)	0.9034 (± 0)	0.8995 (± 0)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Event: Report to Sponsor and CI within 24 hours
Suspected Unexpected Serious Adverse Reaction: Record, assess and report to Sponsor and CI within 24 hours. Report to Reg Authorities within 7 (if fatal/life threatening) / 15 days.

Adverse event reporting additional description:

Please note that many Non-Serious Adverse Events were routinely collected and have been reported as secondary outcome measures. Please refer to End Points for further details. Only those AEs not collected as secondary outcomes have been listed here here.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	1.0

Reporting groups

Reporting group title	Carbetocin

Reporting group description:

This group were randomised to receive Carbetocin

Reporting group title	Syntocinon

Reporting group description:

The group was randomised to receive Syntocinon

Reporting group title	Syntometrine

Reporting group description:

The group was randomised to receive Syntometrine

Serious adverse events	Carbetocin	Syntocinon	Syntometrine
Total subjects affected by serious adverse events			
subjects affected / exposed	63 / 1885 (3.34%)	73 / 1869 (3.91%)	63 / 1884 (3.34%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Tachycardia	Additional description: 'Occurrences causally related to treatment number', refers to Severe Adverse Events that were deemed to have been 'possibly' related to study drug.		
subjects affected / exposed	0 / 1885 (0.00%)	1 / 1869 (0.05%)	0 / 1884 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Laporatomy	Additional description: 'Occurrences causally related to treatment number', refers to Severe Adverse Events that were deemed to have been 'possibly' related to study drug.		
subjects affected / exposed	0 / 1885 (0.00%)	0 / 1869 (0.00%)	1 / 1884 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pregnancy, puerperium and perinatal conditions			
Postpartum haemorrhage	Additional description: 'Occurrences causally related to treatment number', refers to Severe Adverse Events that were deemed to have been 'possibly' related to study drug.		
subjects affected / exposed	53 / 1885 (2.81%)	68 / 1869 (3.64%)	57 / 1884 (3.03%)
occurrences causally related to treatment / all	17 / 53	15 / 68	10 / 57
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Stroke	Additional description: 'Occurrences causally related to treatment number', refers to Severe Adverse Events that were deemed to have been 'possibly' related to study drug.		
subjects affected / exposed	2 / 1885 (0.11%)	1 / 1869 (0.05%)	0 / 1884 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia	Additional description: 'Occurrences causally related to treatment number', refers to Severe Adverse Events that were deemed to have been 'possibly' related to study drug.		
subjects affected / exposed	2 / 1885 (0.11%)	2 / 1869 (0.11%)	1 / 1884 (0.05%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 1885 (0.11%)	1 / 1869 (0.05%)	1 / 1884 (0.05%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma	Additional description: 'Occurrences causally related to treatment number', refers to Severe Adverse Events that were deemed to have been 'possibly' related to study drug.		
subjects affected / exposed	1 / 1885 (0.05%)	0 / 1869 (0.00%)	0 / 1884 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Numbness	Additional description: 'Occurrences causally related to treatment number', refers to Severe Adverse Events that were deemed to have been 'possibly' related to study drug.		
subjects affected / exposed	0 / 1885 (0.00%)	1 / 1869 (0.05%)	1 / 1884 (0.05%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain	Additional description: 'Occurrences causally related to treatment number', refers to Severe Adverse Events that were deemed to have been 'possibly' related to study drug.		

subjects affected / exposed	0 / 1885 (0.00%)	0 / 1869 (0.00%)	1 / 1884 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Allergy	Additional description: 'Occurrences causally related to treatment number', refers to Severe Adverse Events that were deemed to have been 'possibly' related to study drug.		
subjects affected / exposed	0 / 1885 (0.00%)	0 / 1869 (0.00%)	1 / 1884 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Carbetocin	Syntocinon	Syntometrine
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 1885 (0.11%)	7 / 1869 (0.37%)	1 / 1884 (0.05%)
General disorders and administration site conditions			
Cough	Additional description: Coughing/tickly chest		
subjects affected / exposed	0 / 1885 (0.00%)	0 / 1869 (0.00%)	1 / 1884 (0.05%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 1885 (0.05%)	0 / 1869 (0.00%)	0 / 1884 (0.00%)
occurrences (all)	1	0	0
Fainting			
subjects affected / exposed	0 / 1885 (0.00%)	4 / 1869 (0.21%)	1 / 1884 (0.05%)
occurrences (all)	0	4	1
Ear and labyrinth disorders			
Crackling Sensation			
subjects affected / exposed	1 / 1885 (0.05%)	0 / 1869 (0.00%)	0 / 1884 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Twitch			
subjects affected / exposed	1 / 1885 (0.05%)	1 / 1869 (0.05%)	0 / 1884 (0.00%)
occurrences (all)	1	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 April 2015	Amendment 1 1. Sending post-natal follow up questionnaire to participants by post, if not able to contact participant by telephone 2. Prolongation of total predicted recruitment period to 24 months (from 16-18 months) 3. Recruiting participants from 20+ weeks gestation (instead of 36+ weeks), providing the woman feels she has had adequate time to read and consider information contained within the Patient Information Leaflet).
18 August 2015	Amendment 2 Alteration of exclusion criteria Alteration of intrapartum blood pressure threshold at which participant is withdrawn from study Addition of epilepsy as an exclusion criterion Addition of The Great Western Hospital, Swindon, as a participating site
19 October 2015	Amendment 3 Slight alteration of the phrasing of one part of Patient Information Sheet to ensure that the leaflet also accurately reflects "routine clinical care" at University Hospitals Bristol NHS Foundation Trust. Change in the name of Principal Investigator at North Bristol NHS Trust, to cover a period of absence for maternity leave.
15 September 2016	Amendment 4 Change to the recruitment strategy to include the use of participant identification centres (PIC) Addition of Weston Area Health NHS Trust as a PIC for University Hospitals Bristol
18 April 2018	Amendment 5 Change in the name of principal Investigator at Royal United Hospitals, Bath. Change to the Patient Information Sheet and Patient Information Leaflet to reflect that the injection can be also given in the arm. Addition of more information to the protocol with regards to the statistical analysis plan, health economics evaluation, variables and secondary outcomes. The use of oxytocin infusion to augment or induce labour and the administration of terbutaline during the 2nd stage of labour has been changed from secondary outcomes to variables.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported