Clinical trial results:
A pragmatic group sequential placebo controlled randomised trial to determine the effectiveness of Glyceryl trinitrate for retained placenta (GOT-IT Trial)

Summary

EudraCT number	2013-003810-42
Trial protocol	GB
Global end of trial date	03 October 2017

Results information

Result version number	v1 (current)
This version publication date	30 March 2019
First version publication date	30 March 2019

Trial information

Trial identification

Sponsor protocol code	Version8.0; 27/04/2016

Additional study identifiers

ISRCTN number	ISRCTN88609453
ClinicalTrials.gov id (NCT number)	NCT02085213
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	NHS Lothian and University of Edinburgh
Sponsor organisation address	47 Little France Crescent, Edinburgh, United Kingdom, EH16 4TJ
Public contact	Fiach O'Mahony, ACCORD , 44 1312429418, researchgovernance@ed.ac.uk
Scientific contact	Fiach O'Mahony, ACCORD, 44 1312429418, researchgovernance@ed.ac.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	22 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 July 2017
Global end of trial reached?	Yes
Global end of trial date	03 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary research objectives of the internal pilot RCT are:
1) To demonstrate trial processes for approaching women, gaining consent, randomising, treating and assessing outcomes are optimal, and to implement improvements as required;
2) To determine achievable recruitment rates;
3) To determine the likely effect size, to inform a calculation on whether the planned sample size can be reduced whilst maintaining study power;
4) To pilot and modify if required the post-partum questionnaires (assessment of patient satisfaction and collection of health service use outcomes).

The primary research objectives of the substantive GOT-IT RCT are:
1) To determine the clinical effectiveness of sublingual GTN in treating RP and avoiding MROP in women with vaginal delivery following failure of current management (defined as a third stage of labour lasting more than 30 mins after active management or 60 mins after physiological followed by active management respectively) (clinical domain);

Protection of trial subjects:

All potential eligible subjects were screened before they were entered into the trial.

They had the following safety assessments performed.

1. Medical history was obtained.
2. Concomitant medications were checked.
3. Blood pressure, heart rate and temperature were recorded at baseline, 5 and 15 minutes post-administration of study medication.
4. Blood loss was captured from the time the study medication was administered until the woman was moved to the post natal area.
5. Adverse events were reported.

Background therapy:

Study participants had management of the third stage of labour as per current clinical practice which would normally include oxytocin and/or syntometrine.

Evidence for comparator:

Small studies have suggested that nitric oxide donors such as glyceryl trinitrate (GTN) may be an effective treatment for RP. Six studies report that administration of GTN intravenously or via a sublingual tablet was effective in relaxing the uterus to facilitate insertion of the examining hand for MROP or in facilitating delivery of the placenta by controlled cord traction.

Actual start date of recruitment	13 October 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: 1104
Worldwide total number of subjects	1104
EEA total number of subjects	1104

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)	1104
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

October 2014 through July 2017, 29 UK maternity units.

Pre-assignment

Screening details:

Women with retained placenta who fulfil the inclusion criteria and do not meet exclusion criteria will be eligible for study entry following informed consent. 1671 screened, 1107 randomised, 3 post-randomisation exclusions, ITT 1104.

Period 1

Period 1 title	Overall trial (overall period)
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:

All members of the team were blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention

Arm description:

Sublingual GTN spray

Arm type	Experimental
Investigational medicinal product name	GTN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sublingual spray
Routes of administration	Sublingual use

Dosage and administration details:

800mcg;2 puffs sublingual

Arm title	Comparator

Arm description:

Comparator

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sublingual spray
Routes of administration	Sublingual use

Dosage and administration details:

2 puffs sublingual comparator spray

Number of subjects in period 1	Intervention	Comparator
Started	541	563
Completed	535	556
Not completed	6	7
Physician decision	5	7
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	1104	1104	
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)	1104	1104	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
all female			
Units: Subjects			
Female	1104	1104	
Male	0	0	

Subject analysis sets	
Subject analysis set title	Full data
Subject analysis set type	Intention-to-treat

Subject analysis set description:
Intention to treat

Reporting group values	Full data		
Number of subjects	1104		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	1104		
From 65-84 years	0		
85 years and over	0		

Gender categorical			
all female			
Units: Subjects			
Female	1104		
Male	0		

End points

End points reporting groups	
Reporting group title	Intervention
Reporting group description: Sublingual GTN spray	
Reporting group title	Comparator
Reporting group description: Comparator	
Subject analysis set title	Full data
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intention to treat	

Primary: Need for manual removal of placenta by 15 minutes	
End point title	Need for manual removal of placenta by 15 minutes
End point description: Need for MROP of placenta	
End point type	Primary
End point timeframe: Within 15 minutes of intervention	

End point values	Intervention	Comparator	Full data	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	535	556	1104	
Units: Numbers	535	556	1104	

Attachments (see zip file)	Screen Shot 2019-03-12 at 17.42.29.png

Statistical analyses

Statistical analysis title	Statistical analysis
Statistical analysis description: Analysis of primary outcome	
Comparison groups	Intervention v Comparator
Number of subjects included in analysis	1091
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Odds ratio (OR)
Point estimate	1.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.04

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events and serious adverse events were recorded form the time a participant signs the consent form until the 6 week postnatal outcome assessment point.

Adverse event reporting additional description:

Adverse events are assessed for the following:

1. Seriousness
2. Causality
3. Expectedness
4. Severity

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Active(GTN)
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Active(GTN)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 541 (4.99%)	25 / 563 (4.44%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 541 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Procedural headache			
subjects affected / exposed	0 / 541 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hysterectomy			

subjects affected / exposed	0 / 541 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Postpartum haemorrhage			
subjects affected / exposed	23 / 541 (4.25%)	16 / 563 (2.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retained products of conception			
subjects affected / exposed	1 / 541 (0.18%)	3 / 563 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction	Additional description: Anaphylaxis due to Suxamethonium		
subjects affected / exposed	0 / 541 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Obstructive pancreatitis			
subjects affected / exposed	1 / 541 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Endometritis			
subjects affected / exposed	1 / 541 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 541 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	1 / 541 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection	Additional description: Escheria coli and clostridium difficile infection		
subjects affected / exposed	0 / 541 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Active(GTN)	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	166 / 541 (30.68%)	185 / 563 (32.86%)	
Investigations			
Blood pressure decreased			
subjects affected / exposed	6 / 541 (1.11%)	21 / 563 (3.73%)	
occurrences (all)	0	0	
Tachycardia			
subjects affected / exposed	5 / 541 (0.92%)	6 / 563 (1.07%)	
occurrences (all)	0	0	
Blood pressure increased			
subjects affected / exposed	4 / 541 (0.74%)	0 / 563 (0.00%)	
occurrences (all)	0	0	
Full blood count	Additional description: Uncoagulated full blood count sample		
subjects affected / exposed	1 / 541 (0.18%)	0 / 563 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Perineal injury			
subjects affected / exposed	1 / 541 (0.18%)	1 / 563 (0.18%)	
occurrences (all)	0	0	
Vascular disorders			
Deep vein thrombosis	Additional description: Potential deep vein thrombosis		
subjects affected / exposed	1 / 541 (0.18%)	0 / 563 (0.00%)	
occurrences (all)	0	0	
Pregnancy, puerperium and perinatal conditions			

Postpartum haemorrhage			
subjects affected / exposed	166 / 541 (30.68%)	175 / 563 (31.08%)	
occurrences (all)	0	0	
Placenta accreta			
subjects affected / exposed	0 / 541 (0.00%)	1 / 563 (0.18%)	
occurrences (all)	0	0	
Retained products of conception	Additional description: Postnatal readmission for retained products		
subjects affected / exposed	0 / 541 (0.00%)	1 / 563 (0.18%)	
occurrences (all)	0	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 541 (0.00%)	4 / 563 (0.71%)	
occurrences (all)	0	0	
Syncope			
subjects affected / exposed	0 / 541 (0.00%)	3 / 563 (0.53%)	
occurrences (all)	0	0	
Dizziness			
subjects affected / exposed	1 / 541 (0.18%)	0 / 563 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Oral discomfort			
subjects affected / exposed	2 / 541 (0.37%)	0 / 563 (0.00%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	1 / 541 (0.18%)	0 / 563 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	0 / 541 (0.00%)	1 / 563 (0.18%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	0 / 541 (0.00%)	1 / 563 (0.18%)	
occurrences (all)	0	0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 541 (0.00%)	1 / 563 (0.18%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			

Rash	Additional description: Facial rash		
subjects affected / exposed	1 / 541 (0.18%)	0 / 563 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Sepsis			
subjects affected / exposed	7 / 541 (1.29%)	10 / 563 (1.78%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 December 2014	Protocol V3.0 Substantial Amendment 2 Change of exclusion criteria from women having an instrumental delivery to women having an instrumental delivery in theatre.
27 April 2016	Protocol V8.0 Substantial Amendment 11 1. The original definition of haemodynamically stable was systolic blood pressure more than 100mmHG and pulse less than 110 beats per minute. This definition was changed to satisfy all there defintions: Haemodynamically stable Heart rate ≤ 119bpm Systolic blood pressure >100mmHg 2. Change in exclusion criteria to allow co-enrolment to exist for CTIMP trials, providing there was a CTIMP-CTIMP agreement between the Sponsors and investigators of each trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28928192

http://www.ncbi.nlm.nih.gov/pubmed/28539111

http://www.ncbi.nlm.nih.gov/pubmed/27245155

http://www.ncbi.nlm.nih.gov/pubmed/27066777