Clinical trial results:
Intrauterine resuscitation during term labor by maternal hyperoxygenation.

Summary

EudraCT number	2015-001654-15
Trial protocol	NL
Global end of trial date	12 April 2018

Results information

Result version number	v1 (current)
This version publication date	09 March 2022
First version publication date	09 March 2022

Trial information

Trial identification

Sponsor protocol code	NL53018.015.15

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Máxima Medisch Centrum
Sponsor organisation address	De Run 4600, Veldhoven, Netherlands, 5504 DB
Public contact	Principal investigator - Professor Guid Oei, Máxima Medisch Centrum, 0031 624225377, guidoei@outlook.com
Scientific contact	Principal investigator - Professor Guid Oei, Máxima Medisch Centrum, 0031 624225377, laurenbullens@gmail.com

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	07 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 April 2018
Global end of trial reached?	Yes
Global end of trial date	12 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objective: the primary objective is to investigate the effect of maternal hyperoxygenation with 100% oxygen on fetal heart rate pattern. We will describe the difference in FHR deceleration depth, duration and frequency, baseline and variability 10 minutes before and after maternal oxygen administration.

Protection of trial subjects:

The non-rebreathing mask used to deliver oxygen fits tight to the nose and mouth, which may cause some discomfort. Patients are allowed to withdraw from the study anytime.

Background therapy:

Co-interventions may be initiated after 10 minutes of oxygen administration without a satisfactory effect on FHR. Co-interventions are 'conventional care', including lateral positioning of the parturient, stop oxytocin infusion, intermittent pushing, intravenous administration of a tocolytic drug or termination of labor by vaginal assisted delivery or caesarean section. In the control group 10 minutes after inclusion in the study 'conventional care' can be applied.

Evidence for comparator:

The control group will receive conventional care (no additional oxygen). The only difference in treatment between the intervention and control group is the use of additional oxygen. Therefore, it is likely that any difference in outcome will be caused by the use of additional oxygen.

Actual start date of recruitment	01 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 117
Worldwide total number of subjects	117
EEA total number of subjects	117

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)	117
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patient recruitment started on March 1st 2016, and was fulfilled on April 30th 2018. Recruitment took place in The Netherlands.

Pre-assignment

Screening details:

All patients eligible to be included in this study were asked to participate when they visited the outpatient's clinic, or when they were admitted to the delivery ward. The total number of women eligible to be included in this study is not clear.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The patient and attending physician/midwife was not blinded to the allocation. Also the attending pediatrician providing Apgar score was not blinded.The investigator analyzing FHR patterns and fECG was blinded. Laboratory results are not influenced by the knowledge of the allocation and therefore laboratory staff did not need to be blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention group

Arm description:

Maternal hyperoxygenation with 100% oxygen at 10 L/min delivered by a non-rebreathing mask (fraction of inspired oxygen 0.80)

Arm type	Experimental
Investigational medicinal product name	Oxygen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour
Routes of administration	Inhalation use

Dosage and administration details:

100% oxygen via non-rebreathing mask from the onset of fetal heart rate abnormalities, until delivery.

Arm title	Control group

Arm description:

The control group will receive conventional care (no additional oxygen).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Intervention group	Control group
Started	57	60
Completed	57	60

Baseline characteristics

Reporting groups	
Reporting group title	Intervention group
Reporting group description:	
Maternal hyperoxygenation with 100% oxygen at 10 L/min delivered by a non-rebreathing mask (fraction of inspired oxygen 0.80)	
Reporting group title	Control group
Reporting group description:	
The control group will receive conventional care (no additional oxygen).	

Reporting group values	Intervention group	Control group	Total
Number of subjects	57	60	117
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	57	60	117
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Maternal age			
Units: years			
median	31.8	30.7	
standard deviation	± 4.2	± 3.4	-
Gender categorical			
Female			
Units: Subjects			
Female	27	34	61
Male	30	26	56
Parity			
Primiparous versus multiparous women			
Units: Subjects			
primiparous women	35	33	68
multiparous women	22	27	49
Fetal sex			
Units: Subjects			
Male	30	26	56
Female	27	34	61
Gestational age			
Gestational age			
Units: days			
median	279	280	
standard deviation	± 9.0	± 8.8	-

Birthweight Units: gram(s)			
median	3510	3541.4	
standard deviation	± 471.7	± 560.2	-
Body mass index			
Maternal body mass index			
Units: kilogram(s)/cubic meter			
median	25	24	
standard deviation	± 4.7	± 5.0	-

End points

End points reporting groups

Reporting group title	Intervention group
Reporting group description:	
Maternal hyperoxygenation with 100% oxygen at 10 L/min delivered by a non-rebreathing mask (fraction of inspired oxygen 0.80)	
Reporting group title	Control group
Reporting group description:	
The control group will receive conventional care (no additional oxygen).	

Primary: Change in fetal heart rate pattern before and after start of the study protocol

End point title	Change in fetal heart rate pattern before and after start of the study protocol
End point description:	
End point type	Primary
End point timeframe:	
10 minutes before the start of the study protocol compared to 5-15 minutes after the start of the study protocol.	

End point values	Intervention group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	35		
Units: Improvement of FHR				
Deterioration FHR	3	12		
Equal FHR	28	22		
Improvement FHR	5	1		

Statistical analyses

Statistical analysis title	Changes in FHR Odds radio
Comparison groups	Control group v Intervention group
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Odds ratio (OR)
Point estimate	5.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.7
upper limit	19.1

Secondary: 1-minute Apgar score

End point title	1-minute Apgar score

End point description:

End point type	Secondary

End point timeframe:

1 minute after birth

End point values	Intervention group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	60		
Units: number				
1 minute AS <5	4	4		
1 minute AS > 5	53	56		

Statistical analyses

Statistical analysis title	1-minute Apgar score chi-square test
Comparison groups	Control group v Intervention group
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 1
Method	Chi-squared

Secondary: 5-minute Apgar score

End point title	5-minute Apgar score

End point description:

End point type	Secondary

End point timeframe:

5 minutes after birth

End point values	Intervention group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	60		
Units: Number				
5-minute AS <7	1	3		
5-minute AS >7	56	57		

Statistical analyses

Statistical analysis title	5-minute Apgar score Fisher's exact
Comparison groups	Intervention group v Control group
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.62
Method	Fisher exact

Secondary: Median arterial umbilical cord pH

End point title	Median arterial umbilical cord pH

End point description:

End point type	Secondary

End point timeframe:

Generally umbilical cord pH is estimated <15 minutes after birth

End point values	Intervention group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	53		
Units: pH				
median (inter-quartile range (Q1-Q3))	7.22 (7.19 to 7.26)	7.20 (7.16 to 7.27)		

Statistical analyses

Statistical analysis title	Medium arterial pH Mann-Whitney
Comparison groups	Intervention group v Control group

Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.35
Method	Wilcoxon (Mann-Whitney)

Secondary: Median venous umbilical cord pH

End point title	Median venous umbilical cord pH

End point description:

End point type	Secondary

End point timeframe:

Generally umbilical cord pH is estimated < 15 minutes after birth

End point values	Intervention group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	60		
Units: pH				
median (inter-quartile range (Q1-Q3))	7.30 (7.26 to 7.34)	7.30 (7.26 to 7.35)		

Statistical analyses

Statistical analysis title	Median venous pH Mann-Whitney
Comparison groups	Intervention group v Control group
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.94
Method	Wilcoxon (Mann-Whitney)

Secondary: Arterial base excess

End point title	Arterial base excess

End point description:

End point type	Secondary

End point timeframe:

Umbilical cord blood values are generally estimated < 15 minutes after birth.

End point values	Intervention group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	51		
Units: mmol/l				
median (inter-quartile range (Q1-Q3))	-6 (-8 to -3)	-6 (-8 to -4)		

Statistical analyses

Statistical analysis title	Arterial base excess Mann-Whitney
Comparison groups	Intervention group v Control group
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.69
Method	Wilcoxon (Mann-Whitney)

Secondary: Arterial pCO2 umbilical cord blood

End point title	Arterial pCO2 umbilical cord blood

End point description:

End point type	Secondary

End point timeframe:

Umbilical cord blood values are generally estimated < 15 minutes after birth.

End point values	Intervention group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	52		
Units: mmHg				
median (inter-quartile range (Q1-Q3))	56 (51.5 to 59.5)	57 (52 to 62)		

Statistical analyses

Statistical analysis title	Arterial pCO2 Mann-Whitney
Comparison groups	Intervention group v Control group

Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.54
Method	Wilcoxon (Mann-Whitney)

Secondary: Arterial malondialdehyde

End point title	Arterial malondialdehyde

End point description:

End point type	Secondary

End point timeframe:

Umbilical cord blood values are generally estimated < 15 minutes after birth.

End point values	Intervention group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	48		
Units: umol/l				
median (inter-quartile range (Q1-Q3))	4.45 (3.68 to 5.35)	4.15 (3.40 to 4.75)		

Statistical analyses

Statistical analysis title	Arterial malondialdehyde Mann-Whitney
Comparison groups	Intervention group v Control group
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.15
Method	Wilcoxon (Mann-Whitney)

Secondary: Venous malondialdehyde

End point title	Venous malondialdehyde

End point description:

End point type	Secondary

End point timeframe:

Umbilical cord blood values are generally estimated < 15 minutes after birth.

End point values	Intervention group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	54		
Units: umol/l				
arithmetic mean (standard deviation)	4.67 (± 1.27)	4.38 (± 1.15)		

Statistical analyses

Statistical analysis title	Venous malondialdehyde independent T-test
Comparison groups	Intervention group v Control group
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.21
Method	t-test, 2-sided

Secondary: NICU admission	
End point title	NICU admission
End point description: Neonatal Intensive Care Unit admission	
End point type	Secondary
End point timeframe: Directly after birth	

End point values	Intervention group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	60		
Units: number	1	2		

Statistical analyses

Statistical analysis title	NICU admission s Fisher's exact
Comparison groups	Intervention group v Control group

Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 1
Method	Fisher exact

Secondary: Episiotomy for all indications

End point title	Episiotomy for all indications

End point description:

End point type	Secondary

End point timeframe:

Second stage of labor

End point values	Intervention group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	60		
Units: number	30	33		

Statistical analyses

Statistical analysis title	Episiotomy all indications Chi-squared
Comparison groups	Intervention group v Control group
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.8
Method	Chi-squared

Secondary: Episiotomy for fetal indication

End point title	Episiotomy for fetal indication

End point description:

End point type	Secondary

End point timeframe:

Second stage of labor

End point values	Intervention group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	60		
Units: number	17	27		

Statistical analyses

Statistical analysis title	Episiotomy for fetal indication Chi-squared
Comparison groups	Intervention group v Control group
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.09
Method	Chi-squared

Secondary: Assisted delivery for all indications

End point title	Assisted delivery for all indications

End point description:

End point type	Secondary

End point timeframe:

Second stage of labor

End point values	Intervention group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	60		
Units: number	7	9		

Statistical analyses

Statistical analysis title	Assisted delivery all indications Chi-squared
Comparison groups	Intervention group v Control group
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.67
Method	Chi-squared

Secondary: Assisted delivery for fetal indication

End point title	Assisted delivery for fetal indication

End point description:

End point type	Secondary

End point timeframe:

Second stage of labor.

End point values	Intervention group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	60		
Units: Number	4	6		

Statistical analyses

Statistical analysis title	Assisted delivery fetal indication Fisher's exact
Comparison groups	Intervention group v Control group
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.74
Method	Fisher exact

Secondary: Active second stage of labor

End point title	Active second stage of labor

End point description:

End point type	Secondary

End point timeframe:

Second stage of labor.

End point values	Intervention group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	60		
Units: minutes				
median (inter-quartile range (Q1-Q3))	35 (20 to 64)	25 (14 to 58)		

Statistical analyses

Statistical analysis title	Active second stage of labor Mann-Whitney
Comparison groups	Intervention group v Control group
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.32
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Within 15 days after the sponsor has first knowledge of the serious adverse events. SAEs that result in death or are life threatening not later than 7 days after the responsible investigator has first knowledge of the adverse event.

Assessment type	Systematic

Dictionary used

Dictionary name	ToetsingOnline
Dictionary version	NA

Reporting groups

Reporting group title	Control group
Reporting group description: -	
Reporting group title	Intervention group

Reporting group description: -

Serious adverse events	Control group	Intervention group	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 60 (3.33%)	1 / 44 (2.27%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Respiratory disorder neonatal	Additional description: NICU-admissions		
subjects affected / exposed	2 / 60 (3.33%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Control group	Intervention group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 60 (50.00%)	25 / 44 (56.82%)	
Surgical and medical procedures			
Caesarean section	Additional description: Prolonged hospital stay due to secondary cesarean section		
subjects affected / exposed	1 / 60 (1.67%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
Cardiac disorders			

Hypertension	Additional description: Hypertension or pre-eclampsia		
subjects affected / exposed	2 / 60 (3.33%)	0 / 44 (0.00%)	
occurrences (all)	2	0	
Pregnancy, puerperium and perinatal conditions			
Meconium stain	Additional description: Prolonged observation neonate because of Apgar Score 4/7/9 and meconium-stained amniotic fluid		
subjects affected / exposed	1 / 60 (1.67%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Moaning neonatal	Additional description: Observation neonate due to moaning after vacuum-assisted delivery		
subjects affected / exposed	1 / 60 (1.67%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Streptococcus test positive			
subjects affected / exposed	1 / 60 (1.67%)	3 / 44 (6.82%)	
occurrences (all)	1	3	
Apgar score low	Additional description: Prolonged observation neonate because of Apgar Score 1/6/8		
subjects affected / exposed	2 / 60 (3.33%)	0 / 44 (0.00%)	
occurrences (all)	2	0	
SSRI use mother	Additional description: Prolonged observation neonate due to birth >24h after rupture of membranes and due to use of medication mother (Selective serotonin reuptake inhibitors)		
subjects affected / exposed	1 / 60 (1.67%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
Premature baby	Additional description: Prolonged observation neonate due to premature delivery with glucose checks neonate because of small for gestational age		
subjects affected / exposed	2 / 60 (3.33%)	0 / 44 (0.00%)	
occurrences (all)	2	0	
Small for dates baby	Additional description: Prolonged observation neonate with glucose checks neonate because of small for gestational age.		
subjects affected / exposed	3 / 60 (5.00%)	6 / 44 (13.64%)	
occurrences (all)	3	6	
Infection susceptibility increased	Additional description: Prolonged observation neonate due to birth >24h after rupture of membranes of maternal fever during labor		
subjects affected / exposed	12 / 60 (20.00%)	6 / 44 (13.64%)	
occurrences (all)	12	6	
Macrosomia	Additional description: Prolonged observation neonate with glucose checks neonate because of large for gestational age.		
subjects affected / exposed	8 / 60 (13.33%)	8 / 44 (18.18%)	
occurrences (all)	8	8	
Puerperal infection			

subjects affected / exposed	1 / 60 (1.67%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
Nervous system disorders			
Postspinal headache			
subjects affected / exposed	0 / 60 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Post partum hemorrhage	Additional description: Prolonged hospital stay because of postpartum hemorrhage of 2.4 liter due to vaginal tear and uterine atony. Hemoglobin postpartum 3.6 mmol/l for which the patient received 3 packed cells		
subjects affected / exposed	0 / 60 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
neonatal anemia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Bladder dysfunction	Additional description: Prolonged hospital stay due to urine retention of the mother		
subjects affected / exposed	2 / 60 (3.33%)	2 / 44 (4.55%)	
occurrences (all)	2	2	
Metabolism and nutrition disorders			
Hyperbilirubinaemia neonatal			
subjects affected / exposed	0 / 60 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2015	Inclusion criteria changed to including small for gestational age fetuses (estimated fetal weight < p10)
15 March 2016	Implementation of a modified method to monitor fECG.
23 March 2017	Asking patients enrolled in the study to fulfill a short questionnaire about how they feel about their labor.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

13 women in the intervention group did not receive oxygen administration for >5 minutes.
20 women were included while having exclusion criteria.
Healthcare providers were not blinded for the allocation to the intervention or control group.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33345953

http://www.ncbi.nlm.nih.gov/pubmed/33049730