Neonatal resuscitation: comparing sustained inflations to standard practice

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Protocol for: Neonatal resuscitation: comparing sustained inflations to standard practice

A prospective randomised controlled trial assessing the efficacy of sustained inflations in neonatal resuscitation compared to repeated shorter inflation breaths

Sponsor

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Study Synopsis

Title	**Neonatal resuscitation: comparing sustained inflations to repeated shorter inflation breaths**
Protocol Short Title/Acronym	Neonatal Resuscitation: sustained inflation
Protocol Version number and Date	4 11/1/18
Study Phase if not mentioned in title	
Is the study a Pilot?	No
Study Duration	12 months
Methodology	Randomised controlled trial
Sponsor name	Mr Keith Brennan/Ms Liba Stones
Chief Investigator	Professor Anne Greenough
REC number	16 LO 1718
Medical condition or disease under investigation	Need for resuscitation at delivery in babies born prematurely
Purpose of clinical trial	To assess whether 15 second inflations are more effective at stimulating spontaneous breathing than five shorter inflation breaths of 2-3 seconds.
Primary objective	To assess whether sustained inflations provoke active inflations sooner during resuscitation than repeated shorter inflation breaths
Secondary objective (s)	To assess whether sustained inflations improve tidal volume exchange and end tidal carbon dioxide levels compared to repeated shorter inflation breaths, and to collect data regarding any adverse outcomes.
Number of Subjects/Patients	48 +
Trial Design	Randomised controlled trial
Endpoints	Equal distribution of gestational age between groups
Main Inclusion Criteria	Any baby born <34/40 requiring resuscitation at delivery
Statistical Methodology and Analysis	Non-parametric statistics

Glossary of Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
EC	European Commission
GAfREC	Governance Arrangements for NHS Research Ethics Committees
ICF	Informed Consent Form
ISRCTN	International Standard Randomised Controlled Trial Number
MA	Marketing Authorisation
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principle Investigator
QA	Quality Assurance
QC	Quality Control
Participant	An individual who takes part in a clinical trial
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee

1. Introduction

Around 10% of newborns will require some form of assistance after delivery, with babies born more prematurely more likely to require resuscitation.[1]

Current UK guidelines advise initial resuscitation with the delivery of five 'inflation breaths' lasting 2-3 seconds with peak inflation pressure of 30cmH2O (20-25cm H2O in premature neonates).[2] Previous studies have shown that despite resuscitation training, clinicians in both simulated and real resuscitation scenarios do not deliver the recommended duration of inflation breaths[3]. This, combined with leaks around the facemask often being as large as 50% or greater, contributes to low expired tidal volumes during resuscitation, thus increasing the likelihood of hypoxia and delay in establishing effective respiration.

The use of sustained inflations (up to 15 seconds), rather than intermittent shorter inflation breaths, has shown promising results, with reduction in the need for intubation, and the need for and duration of mechanical ventilation.[4–7] Around 30% of units in Germany use sustained inflations as first line delivery room management, as do many other hospitals around the world.[8] Resuscitation guidelines from the USA, UK and Europe suggest that sustained inflations should be researched further.[9,10]

Several studies have shown that for several lengths of inflation breaths, the expired tidal volume achieved is higher if the baby makes respiratory effort during the inflation (active inflation),[3,11,12] and that stimulation of spontaneous respiratory effort is a key part in establishing an FRC, enabling spontaneous breathing, and increasing the likelihood of successful resuscitation.

To date, there are no studies directly comparing whether prolonged inflations are more successful at provoking an inspiration than other methods of resuscitation. We therefore aim to compare a 15 second sustained inflation to repeated shorter inflations to determine which is more effective.

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2 Trial Objectives, Design and Statistics

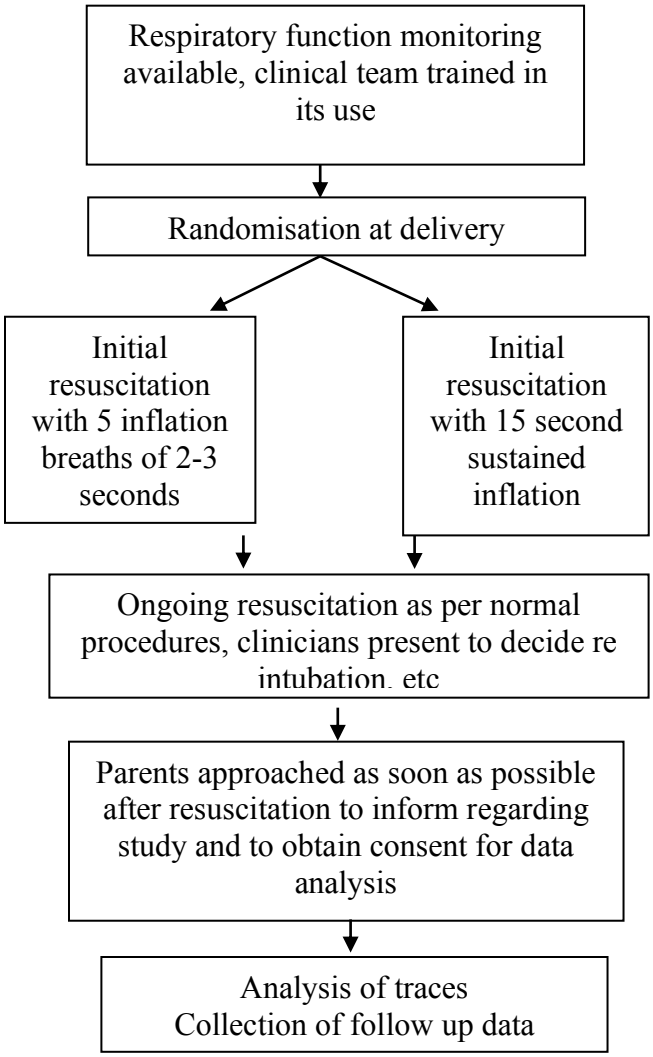
2.1. Trial Objectives

To assess whether a 15 second inflation are more effective at stimulating spontaneous breathing than five shorter breaths of 2-3 seconds, evidenced by a greater number of active inflations and superior tidal volume exchange and end tidal carbon dioxide levels.

2.2 Trial Design & Flowchart

Randomised controlled trial.

2.3 Trial Flowchart



3. Sample Size, Selection and Withdrawal of Subjects

We have previously demonstrated that active compared to passive inflations during resuscitation at least double expiratory tidal volumes and end tidal CO2 levels. (An active inflation is one where the baby makes inspiratory effort during a mechanical inflation.) During resuscitation with short inflations, all infants had an active inflation by 50 seconds, but the active inflation occurred earlier in those who received longer rather than shorter mechanical inflations. We therefore postulate that over the first minute of resuscitation the total expiratory tidal volume (minute volume) will be 25% higher in the prolonged inflation group. Randomisation of 40 infants will allow us to detect one standardised difference in the minute volume between the two groups with 90% power at the 5% level. The standard deviation in our previous cohort in minute volume was 71mls/min/kg, that is 25% of the maximum minute volume achieved in our previous cohort.

At reaching the prespecified sample size we have a two week discrepancy in gestational age between the two groups, and therefore we will continue to recruit to the study until this is balanced. We anticipate that around 60 infants will be required but this will be reviewed after every 4 babies to be recruited.

Inclusion Criteria
Infants born less than 34 weeks of gestation requiring resuscitation at delivery.

Exclusion Criteria
Major congenital abnormalities

Criteria for Premature Withdrawal
Withdrawal of parental consent

4. Study procedures

Informed Consent Procedures
Preterm delivery may often occur without significant prior warning. When women are in preterm labour, it may be inappropriate to approach them regarding research at this potentially distressing time, particularly as this may be very close to the point of delivery.
We therefore intend to conduct this study as emergency research without prior informed consent, and will approach parents as soon as is practical after delivery to explain the research and to gain consent for analysis of resuscitation data and collection of further data.
Information will be displayed on the antenatal wards regarding research without prior consent and contact details if any parents wish to discuss this.

4.1 Screening Procedures
There are no study specific screening procedures prior to entry into the study.

4.2 Randomisation Procedures
A random number generator will be used and allocations concealed in sealed opaque envelopes, opened immediately when it is deemed that resuscitation is required.

4.3 Schedule of Events for each visit
Infants randomised to the routine care group will receive resuscitation as per NLS protocols, with the addition of respiratory function monitoring. Infants randomised to the sustained inflation group will receive a 15 second sustained inflation at 25cmH_2O in place of the five inflation breaths and this will be repeated in situations where, under normal circumstances, the five inflation breaths would be repeated (e.g. no chest rise seen.) The decision to initially resuscitate via facemask or to immediately intubate will be taken on usual clinical grounds, as will any subsequent decisions to intubate, perform chest compressions, or deliver medications. Resuscitation will otherwise proceed as per normal practice and, as above, the decision to intubate etc will be taken on normal clinical grounds by the team performing the resuscitation.

4.4 Follow up Procedures
Data regarding rates of pneumothorax, patent ductus arteriosus, intraventricular haemorrhage, need for mechanical ventilation in the first 72 hours of life, and mortality will be recorded.

4.5 Radiology Assessments *(not applicable)*
Not applicable

4.6 End of Study Definition

Following completion of the measurements and analysis of the results of the required number of infants, the REC will be informed that the study has been completed.

5. Laboratories (not applicable)

6. Assessment of Safety
Some studies have shown small, non-significant trends towards increased incidence of pneumothorax and intraventricular haemorrhage with sustained inflations. Another trial has shown a reduction in the incidence of air leak with sustained inflation, and animal studies have demonstrated improved stabilisation of cerebral blood flow with sustained inflation. Meta-analysis of four trials has shown an increase in the occurrence of patent ductus arteriosus requiring treatment, but these trials were heterogenous in terms of the oxygen concentration used and length and pressure of sustained inflation. Sustained inflations have not previously been compared to five shorter inflation breaths lasting 2-3 seconds. Sustained inflations are used as a routine standard of care in many hospitals worldwide.

6.1 Ethics Reporting

Reports of related and unexpected serious adverse events will be submitted to the Main REC within 15 days of the chief investigator becoming aware of the event, using the NRES template. The parents will be informed of any events as soon as possible and be provided with an opportunity to meet with clinical and research team. The results of any reports or investigations relating to the events will also be communicated to the parents in writing.

7. Trial Steering Committee

8. Ethics & Regulatory Approvals
We will make an application via IRAS for HRA and NHS REC review and approval.

Confidentiality

Analysis of the data will take place at King's College Hospital and is to be undertaken by a clinical research fellow and by Professor Greenough, the chief investigator.

Each patient will be assigned a unique patient identifier, under which patient data will be anonymously stored on a password protected computer. All paper copies containing patient identifiable data will be kept in a locked filing cabinet until the patients are 25 years of age. Only the principal investigator and research fellow involved in the study will have access to the data, the principal investigator will act as custodian.

Case Report Form

Elements included in each case report form (CRF):
-Unique patient identifier
-Date of parental consent

-Eligibility criteria checklist
-Date of resuscitation
-Any adverse events noted

Completion of the CRF will be the responsibility of the clinical research fellow.

Record Retention and Archiving
Records will be held in a locked filing cabinet located within the research office based at the neonatal unit of Kings College Hospital. Access is limited to the clinical research fellow and Chief Investigator.

Compliance
The CI will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, Trust and Research Office policies and procedures and any subsequent amendments.

Clinical Governance Issues

-Audit and Inspection
Accurate records of all research activity including copies of the consent forms and completed case report forms will be safely stored and audited for compliance if requested.

-Non-Compliance

The sponsor will maintain a log of the non-compliances to ascertain if there are any trends developing which to be escalated. The sponsor will assess the non-compliances and action a timeframe in which they need to be dealt with. Each action will be given a different timeframe dependant on the severity. If the actions are not dealt with accordingly, the R&D Office will agree an appropriate action, including an on-site audit.

10. Finance and Publication Policy

Appendix 1 – Information with regards to Safety Reporting in Non-CTIMP Research

	Who	When	How	To Whom
SAE	Chief Investigator	-Report to Sponsor within 24 hours of learning of the event -Report to the MREC within 15 days of learning of the event	SAE Report form for Non-CTIMPs, available from NRES website.	Sponsor and MREC
Urgent Safety Measures	Chief Investigator	Contact the Sponsor and MREC Immediately Within 3 days	By phone Substantial amendment	Main REC and Sponsor Main REC with a

			form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action.	copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt.
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion)	Annual Progress Report Form (non-CTIMPs) available from the NRES website	Main REC
Declaration of the conclusion or early termination of the study	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination) *The end of study should be defined in the protocol*	End of Study Declaration form available from the NRES website	Main REC with a copy to be sent to the sponsor
Summary of final Report	Chief Investigator	Within one year of conclusion of the Research	No Standard Format However, the following Information should be included:- Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to participants	Main REC with a copy to be sent to the sponsor