# Non-CTIMP Study Protocol

## *MONITOR*

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|---|---|
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# LIST OF ABBREVIATIONS

| | |
|---|---|
| **ACCORD** | Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board |
| **AE** | Adverse Event |
| **AR** | Adverse Reaction |
| **CI** | Chief Investigator |
| **CRF** | Case Report Form |
| **GCP** | Good Clinical Practice |
| **ICH** | International Conference on Harmonisation |
| **PI** | Principal Investigator |
| **QA** | Quality Assurance |
| **REC** | Research Ethics Committee |
| **SAE** | Serious Adverse Event |
| **SAR** | Serious Adverse Reaction |
| **SOP** | Standard Operating Procedure |
| **SUSAR** | Suspected Unexpected Serious Adverse Reaction |

# 1 INTRODUCTION

## 1.1 BACKGROUND

The aim of oxygen therapy is to deliver sufficient oxygen to tissues to maintain tissue function and avoid adverse consequences, whilst minimising oxidative stress and oxygen toxicity. It is unclear how best to achieve this balance in premature infants, who are at high risk of developing oxygen-related morbidities because of their relative lack of antioxidant protection.

Oxygenation can be monitored by measurement of pulse oximeter oxygen saturation ($SpO_2$), which estimates the percentage of haemoglobin (an oxygen carrying molecule in red blood cells) binding sites occupied by oxygen, using a transcutaneous monitor to measure transcutaneous partial pressure of oxygen ($TcPO_2$) which is the amount of oxygen diffusing across the skin, or by measuring the partial pressure of oxygen ($PaO_2$) dissolved in arterial blood.

The gold-standard for assessing oxygen levels is accepted to be arterial oxygen tension ($PaO_2$) but measuring this is invasive and it cannot be measured continuously. $SpO_2$ monitoring provides a continuous, non-invasive measure, but $SpO_2$ and $PaO_2$ are related in a complicated, non-linear way. $TcPO_2$ and $PaO_2$ levels correlate well and are related in a linear way.

In the early 2000s a number of cohort studies gave conflicting results about the optimum oxygen range in preterm babies. Therefore consensus was achieved to conduct a prospective meta-analysis of oxygen targeting studies, of sufficient power to test the hypothesis that a strategy of maintaining a functional $SpO_2$ level in a “lower” (85-89%) versus a “higher” (91-95%) range early in the course of extremely low gestational age neonates reduces the incidence of severe ROP without increasing important adverse neonatal outcomes[1]. The Neonatal Oxygenation Prospective Meta-analysis (NeOProM) involved data from the SUPPORT, BOOST II Australia, BOOST NZ, COT, and BOOST II UK trials and was powered to detect a small but important 4% increase in death or severe disability in survivors[2].

Three recent systematic reviews and meta-analyses using data from the five studies that make up the NeOProM collaboration have all revealed a significant increase in the risk of death associated with targeting infants to the lower $SpO_2$ range. Saugstad OD, Aune D[3] found relative risks (RR; 95% CIs) comparing a low versus a high oxygen saturation target were 1.41 (1.14-1.74) for mortality at discharge or at follow-up. Manja and Lakshminrusimha[4] found a significant increase in mortality before hospital discharge in infants targeted to the lower $SpO_2$ range (RR, 1.18 [95% CI, 1.03-1.36]). Askie et al.[5] found a lower $SpO_2$ target range significantly increased the incidence of death at 18 to 24 months corrected age (typical RR 1.16, 95% CI 1.03 to 1.31; typical RD 0.03, 95% CI 0.01 to 0.05; 5 trials, 4873 infants).

As described above, the search for the optimum oxygen level to target preterm infants to is still ongoing. Although there is very good evidence targeting infants to a lower oxygen level results in harm, it is not clear whether the higher target level used in the NeOProM studies achieves the optimum survival advantage.

## 1.2 RATIONALE FOR STUDY

There is still considerable uncertainty about what oxygen levels premature babies should be targeted too. Although there is clear evidence that targeting babies to a lower oxygen saturation (SpO2) level is associated with harm, it is not clear whether we have found the optimum oxygen target level which maximises survival benefit.

We believe the question of oxygen targeting is an important one in neonatology, and this proposal would be a safe and reliable way of characterising the actual oxygen levels achieved at a higher SpO2 target range. We hope the results of this study would inform a larger research study using higher SpO2 limits and powered to analyse clinical outcomes.

Because very high oxygen levels may cause harm (such as increasing the risk of retinopathy of prematurity - a condition that although treatable can affect vision), it is prudent to increase oxygen target limits by small increments, and for a short amount of time. This is why we are proposing a small increase in SpO2 target limits from 90-95% to 92-97%, for a short period (6 hours).

Based on previous research it is very unlikely that these slightly higher ranges will be associated with hyperoxia (high levels of oxygen in the blood), but it is also sensible to monitor oxygen levels by more than just SpO2, as SpO2 is not the best way of measuring hyperoxia. This is why we are proposing to use transcutaneous oxygen monitoring (TcPO2) throughout the study, as previous research has demonstrated TcPO2 is better at detecting hyperoxia than SpO2.

In order to minimise confounding factors, we propose that infants act as their own controls, being randomised either a higher or standard SpO2 target limit, and then crossing over to the other SpO2 target range after 6 hours.

As described above, we feel that the research question is an important one, and our proposal will be able to answer it. We believe this proposal minimises risk to infants. Although previous research has suggested a very high levels of oxygen are associated with increased risk of ROP, there is good evidence to suggest that our proposed slightly higher SpO2 range will not be associated with hyperoxia, and the use of TcPO2 is an additional safety measure. We need to balance the risk of ROP with the very real risk that we are missing the opportunity to reduce mortality in premature babies by not using an SpO2 target range that is high enough to achieve maximum survival advantage.

Written informed consent will be sought from the parents of eligible infants by research staff trained in GCP, and all information will be handled in accordance with Caldicott principles.

# 2 STUDY OBJECTIVES

## 2.1 OBJECTIVES

### 2.1.1 Primary Objective

To discover the percentage time spent above an $SpO_2$ of 97% and below an $SpO_2$ of 90% when infants are targeted to an $SpO_2$ range of 92-97% compared to 90-95%

### 2.1.2 Secondary Objectives

To discover the percentage time spent above a $TcPO_2$ of 80mmHg and below a $TcPO_2$ of 50mmHg when infants are targeted to an $SpO_2$ range of 92-97% compared to 90-95%

To discover the variability in $SpO_2$ (measured by standard deviation) when infants are targeted to an $SpO_2$ range of 92-97% compared to 90-95%

To discover the variability in $TcPO_2$ (measured by standard deviation) when infants are targeted to an $SpO_2$ range of 92-97% compared to 90-95%

In infants who are undergoing $PaO_2$ measurement as part of their routine care describe the PO2 values observed in the two target ranges.

To generate a pooled frequency histogram of percentage time at each $SpO_2$ point between 80 and 100% for infants targeted to an $SpO_2$ range of 92-97% compared to 90-95%

To generate a pooled frequency histogram of percentage time at a TcPO2 of below 30mmHg, 30-39.9mmHg, 40-49.9mmHg, 50-59.9mmHg, 60-69.9mmHg, 70-79.9mmHg, and 80mmHg and above for infants targeted to an $SpO_2$ range of 92-97% compared to 90-95%

# 3 STUDY DESIGN

Summary

This study is a single centre randomised crossover study. Infants born at less than 29 weeks gestation, greater than 48 hours of age and receiving supplementary oxygen would be eligible for inclusion. The study is at the Royal Infirmary of Edinburgh. Total study time is 12 hours for each infant (6 hours at the standard 90-95% range used in our unit, and 6 hours at 92-97%). It is a crossover study with infants acting as their own controls.

A complete list of all monitoring that will be carried out is shown below:

1. SpO2 monitoring

2. TcPO2 monitoring

3. Heart rate monitoring (used to validate SpO2 readings as described below)

4. Arterial gas sampling (only if conducted by the direct care team as part of the routine care of the infant will these be recored. No extra blood samples will be taken as part of the study)

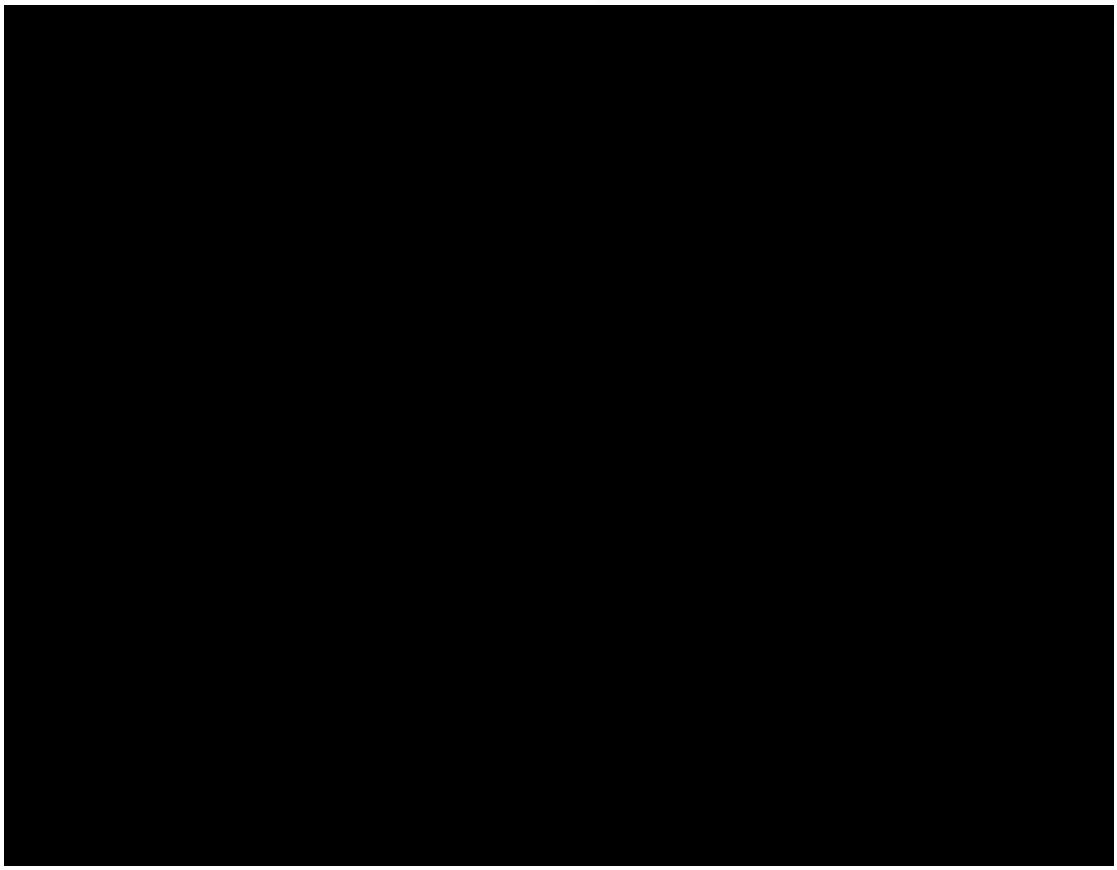
Design

Each infant will be monitored simultaneously with an $SpO_2$ monitor and $TcPo_2$ monitor, with data recording starting from the time the transcutaneous monitor finishes calibrating. $SpO_2$ readings will be downloaded directly from the multiparameter patient monitor. $SpO_2$ will be measured using a Siemens Infinity SC7000 multiparameter monitor (Siemens Medical Systems, Danvers MA). This monitor uses Siemens' Oxisure pulse oximetry technology and Nellcor Oximax (Nellcor Puritan Bennett, CA, USA) saturation probes and incorporates ECG to reduce motion artefact. To reduce the influence of artefact further, data from an infants chest leads (recording heart rate) will also be downloaded. If there is a greater than 10beats per minute difference between heart rate measured from the pulse oximeter and heart rate measured from the chest leads, $SpO_2$ for that time point will be disregarded.

$TcPO_2$ will be measured using a SenTec Digital Monitoring System with OxiVent sensor (SenTec AG, Switzerland, European patent No. 1535055, CE 0120). $TcPO_2$ is calculated by dynamic fluorescence quenching which measures oxygen molecules present in the vicinity of a fluorescent dye incorporated within the sensor surface. The sensor is operated at a constant temperature of 43 degrees Celsius. Control of sensor temperature and application duration are designed to meet all applicable standards and this monitoring device is used routinely in many neonatal units, with transcutaneous monitoring part of the monitoring equipment we use in selected infants in our unit and being transported by our local neonatal transport team. Temperature is supervised by two independent circuits, as well as by the monitor firmware.

Transcutaneous data will be transferred contemporaneously to a bedside PC via the proprietary software V-STATS (with V-CareNeT) version 4.01 (SenTec AG, Ringstrasse 39, CH-4106 Therwill, Switzerland). We will ensure the time on the monitor is synchronised with the time displayed on the electronic patient record system recording $SpO_2$ and heart rate. V-STATS software can identify any spurious spikes in $TcPO_2$ caused by air bubbles and these identified segments of data will be discarded. Artefact has not significantly affected readings during the routine use of this monitor previously on our neonatal unit and with our neonatal transport team. The site of the transcutaneous probe will be rotated on each infant every 2 hours.

$SpO_2$, $TcPO_2$ and heart rate data will be recorded every second. The time of any arterial oxygen samples taken routinely during the study will be recorded from the unit blood gas analyser (ABL800 FLEX, Radiometer, Denmark, 2005).



# 4 STUDY POPULATION

## 4.1 NUMBER OF PARTICIPANTS

A sample of 20 preterm babies born at the Royal Infirmary of Edinburgh meeting the inclusion criteria will be recruited. Because we are obtaining pilot data to inform the design of future studies we do not have a basis for a power calculation

## 4.2 INCLUSION CRITERIA

Infants born at less than 29 weeks gestation
Infants greater than 48 hours of age
Infants who are receiving supplementary oxygen

## 4.3 EXCLUSION CRITERIA

Congenital anomalies that would affect oxygenation (eg. cardiac defects, congenital diaphragmatic hernia)

## 4.4 CO-ENROLMENT

The neonatal unit frequently conducts research projects - both single centre and multicentre projects. There is no contraindication to participating in this research if currently enrolled in another study. We have found that parents greatly appreciate being involved in studies, and are unlikely to be overwhelmed by being approached for multiple studies. Parents are made aware that they are free to decline to participate in any study without giving a reason.

# 5 PARTICIPANT SELECTION AND ENROLMENT

## 5.1 IDENTIFYING PARTICIPANTS

Potential participants would initially be identified by the direct care team.

## 5.2 CONSENTING PARTICIPANTS

The parents of babies born at less than 29 weeks gestation will be approached by a member of the research team and given an information leaflet. If parents then would like to discuss the study further, a member of the research team (with appropriate GCP training) will discuss this with them at their convenience, and ask for consent if they are willing to participate.

### 5.2.1 Withdrawal of Study Participants

Parents will be free to withdraw their infant from study at any time without having to give a reason. As the study involves routinely used equipment and is of short duration it is not anticipated that this will happen.

# 6 STUDY ASSESSMENTS

## 6.1 STUDY ASSESSMENTS

By targeting babies to higher oxygen saturation levels there is a possibility that they will be subjected to higher oxygen levels than previously recommended for short periods. Previous research and audit of our unit's blood gas machine results suggests that at a $SpO_2$ target range of 92 to 97% this is very unlikely, and is in fact more likely to keep babies' within the previously suggested oxygen tension target range. In addition, the use of the transcutaneous monitor with upper limit alarms enabled, mitigates the risk of high $PaO_2$ levels, and the very short study period means infants are only targeted to slightly higher oxygen levels for 6 hours.

Transcutaneous oxygen monitoring is part of routine clinical practice. The use of transcutaneous probes have in the past been associated with transient skin redness in preterm babies' skin (as the probe is heated). Modern devices use a lower temperature than those used in previous research, and probes have safety mechanisms whereby the probe is no longer heated if it is left in place for longer than the recommended time.

# 7 DATA COLLECTION

The study diagram is section 3 details the timepoints and data collected during each study period. Collection of data is contemporaneous and checked for validity as described above. Valid and anonymised $SpO_2$ and $TcPO_2$ will then be used in the analysis.

# 8 STATISTICS AND DATA ANALYSIS

## 8.1 SAMPLE SIZE CALCULATION

This is a pilot study to inform a larger study of $SpO_2$ and possibly $TcO_2$ ranges.

Recruitment is planned to end when 20 babies have been recruited and randomised. Based on the frequency of delivery of preterm babies in our unit we estimate the study to last 1 year.

## 8.2 PROPOSED ANALYSES

For each group we will calculate the percentage of readings above an $SpO_2$ of 97% and below an $SpO_2$ of 92%. These percentages will then be compared between groups by using a Student's T-test.

The variability of $SpO_2$ for each group will be expressed by calculating the standard deviation of all the valid $SpO_2$ data points in each group. Comparison between variability between groups will be performed by Student's T-test.

Pooled $SpO_2$ data from each infant randomised to the 90-95% $SpO_2$ group will then be used to generate time at each $SpO_2$ point for the group as a whole, expressed as a percentage of the total number of valid $SpO_2$ readings. This process will then be repeated for the 92-97% $SpO_2$ target range group.

Pooled $TcPO_2$ data from each infant randomised to the 90-95% $SpO_2$ group will then be used to generate time within the following $TcPO_2$ ranges for the group as a whole: below 30mmHg, 30-39.9mmHg, 40-49.9mmHg, 50-59.9mmHg, 60-69.9mmHg, 70-79.9mmHg, and 80mmHg and above. This will be expressed as a percentage of the total number of valid $TcPO_2$ readings. This process will then be repeated for the 92-97% $SpO_2$ target range group.

# 9 ADVERSE EVENTS

This study uses monitoring equipment that has been used routinely in neonatal units for many years, and therefore the risk of adverse events is small. By targeting babies to higher oxygen saturation levels there is a possibility that they will be subjected to higher oxygen levels than previously recommended for short periods. Previous research and audit of our unit's blood gas machine results suggests that at a $SpO_2$ target range of 92 to 97% this is very unlikely, and is in fact more likely to keep infants within the previously suggested oxygen tension target range. The risk of hyperoxia in infants is mitigated by the short study period and the use of transcutaneous monitoring which detects hyperoxia better than saturation monitoring.

The researcher will be present throughout the short study period for each infant. If the direct care team feel that the additional monitoring equipment is interfering in any way with routine care of the infant, the study will be discontinued in that infant.

## 9.1 DEFINITIONS

This study is not a drug study. The following concerns definitions and reporting of adverse events that may arise due to the study intervention (targeting infants briefly to a slightly higher oxygen saturation range).

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with the study intervention.

An **adverse reaction** (AR) is any untoward and unintended response to the study intervention.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that:

- results in death of the clinical trial participant;
- is life threatening*
- requires in-patient hospitalisation^ or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

*Life-threatening in the definition of an SAE or SAR refers to an event where the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

^Any hospitalisation that was planned prior to randomisation will not meet SAE criteria. Any hospitalisation that is planned post randomisation will meet the SAE criteria.

**A suspected unexpected serious adverse reaction** (SUSAR) is any AR that is classified as serious and is suspected to be caused by the study intervention, that it is not consistent with previous research and hypotheses highlighted in the Study Protocol.

## 9.2 IDENTIFYING AEs AND SAEs

All AEs and SAEs will be recorded from the time a baby commences the first study period until 1 week after the final participant has completed the study. Adverse incidents may include skin redness following the use of transcutaneous probes or periods of hyperoxia.

## 9.3 RECORDING AEs AND SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator will then record all relevant information in the CRF and on the SAE form (if the AE meets the criteria of serious).

Information to be collected includes type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

## 9.4 ASSESSMENT OF AEs AND SAEs

Seriousness, causality, severity and expectedness will be assessed by the Principal Investigator. The Investigator is responsible for assessing each AE.

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

### 9.4.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 10.1.

### 9.4.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the study intervention according to the definitions below.

- Unrelated: where an event is not considered to be related to the study intervention.
- Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study intervention.

### 9.4.3 Assessment of Expectedness

If an event is judged to be an AR, the evaluation of expectedness will be made based on knowledge of the reaction and either the relevant information about the additional monitoring device, or previous research on oxygenation of preterm infants.

The event may be classed as either:

**Expected**: the AR is consistent with the previous experience of the additional monitoring device, or consistent with previous peer-reviewed oxygenation research.

**Unexpected**: the AR is not consistent with the above.

### 9.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE and record this on the CRF or SAE form according to one of the following categories:

**Mild**: an event that is easily tolerated by the infant, not thought to cause discomfort and not interfering with physiological parameters outwith the short study period.

**Moderate**: an event that is sufficiently discomforting or requires short-term intervention or monitoring outwith the study period.

**Severe**: an event that causes severe physiological disturbance, discomfort or that requires long-term follow-up.

Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

## 9.5 REPORTING OF SAEs/SARs/SUSARs

Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD Research Governance & QA Office **immediately or within 24 hours**. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.

The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 10.4.2, Assessment of Causality and 10.4.3, Assessment of Expectedness.

The SAE form will be transmitted by fax to ACCORD on **+44 (0)131 242 9447** or may be transmitted by hand to the office or submitted via email to Safety.Accord@ed.ac.uk. Only forms in a pdf format will be accepted by ACCORD via email.

Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the investigator and request the missing information.

All reports faxed to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

## 9.6 REGULATORY REPORTING REQUIREMENTS

The ACCORD Research Governance & QA Office has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the trial). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD will inform Investigators at participating sites of all SUSARs and any other arising safety information.

An Annual Safety Report/Development Safety Update Report will be submitted, by ACCORD, to the regulatory authorities and RECs listing all SARs and SUSARs.

## 9.7 FOLLOW UP PROCEDURES

After initially recording an AE or recording and reporting an SAE, the Investigator will follow each participant until resolution or death of the participant. Follow up information on an SAE will be reported to the ACCORD office.

AEs still present in participants at the last study visit will be monitored until resolution of the event or until no longer medically indicated.

# 10 OVERSIGHT ARRANGEMENTS

## 10.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

## 10.2 RISK ASSESSMENT

A study specific risk assessment will be performed by representatives of the co-sponsors, ACCORD monitors and the QA group, in accordance with ACCORD governance and sponsorship SOPs. Input will be sought from the Chief Investigator or designee. The outcomes of the risk assessment will form the basis of the monitoring plans and audit plans. The risk assessment outcomes will also indicate which risk adaptions (delete if no adaptations were possible) could be incorporated into to trial design.

## 10.3 STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and, if so, at what frequency.

Risk assessment, if required, will determine if audit by the ACCORD QA group is required. Should audit be required, details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

# 11 GOOD CLINICAL PRACTICE

## 11.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

## 11.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

### 11.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a parent to enroll their infant in the study is voluntary and should be based on a clear understanding of what is involved.

Parents will receive written adequate oral and written information about the study - appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the parents will be performed by the researcher who is GCP trained and will cover all the elements specified in the Participant Information Sheet and Consent Form.

Parents must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. Parents will be given sufficient time to consider the information provided (5 days). It will be emphasized that parents may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. Parents will receive a copy of this document and a copy filed in the Investigator Site File (ISF).

### 11.2.2 Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

### 11.2.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

### 11.2.4 Investigator Documentation

- The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs.

### 11.2.5 GCP Training

The researcher is GCP trained, as indicated in his CV.

### 11.2.6 Confidentiality

Data will be anonymised and stored on an encrypted computer within a locked room. The anonymisation key and consent forms will be stored in a separate keypad accessed room in a locked cabinet. Data will be handled according to Caldicott principles and stored according to Accord SOPs.

### 11.2.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to individuals from the research team treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

# 12 STUDY CONDUCT RESPONSIBILITIES

## 12.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

## 12.2 MANAGEMENT OF PROTOCOL NON COMPLIANCE

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

## 12.3 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

## 12.4 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 3 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

## 12.5 END OF STUDY

The end of study is defined as the last participant's last visit.

The Investigators or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R+D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is

arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot.

A summary report of the study will be provided to the REC within 1 year of the end of the study.

### 12.6 CONTINUATION OF TREATMENT FOLLOWING THE END OF STUDY

The monitoring used in the study is routine within neonatal units and will continue after the end of the study. A decision to change oxygen saturation target limits would only be made after careful consideration of all available peer-reviewed literature.

### 12.7 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

## 13 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

### 13.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team.

## 14 REFERENCES

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