PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A multicentre, randomised controlled, non-inferiority trial, comparing nasal high-flow with nasal continuous positive airway pressure as primary support for newborn infants with early respiratory distress born in Australian non-tertiary special care nurseries (The HUNTER Trial): study protocol
AUTHORS	Manley, Brett; Roberts, Calum; Arnolda, Gaston; Wright, Ian; Owen, Louise; Dalziel, Kim; Foster, Jann; Davis, Peter; Buckmaster, Adam

VERSION 1 - REVIEW

REVIEWER	Michael Dunn Sunnybrook Health Sciences Centre Toronto, Ontario CANADA
REVIEW RETURNED	24-Mar-2017

GENERAL COMMENTS	I appreciate the opportunity to review the protocol submitted by Brett Manley and colleagues where they outline their study comparing nCPAP to nHF as the primary mode of respiratory support in infants born and cared for in a group of non-tertiary NICUs in Australia. This is a pragmatic trial examining the question of whether initial support with nHF leads to similar outcomes than when a baby with respiratory distress is provided with nCPAP. They have set up the study as a non-inferiority trial as they have done before based on the widespread view that if non-inferior to nCPAP, nHF would be a preferable mode of respiratory support in most cases. This type of design is being used more frequently in recent years and has been successfully employed in previous trials designed to determine the place on nHF in NICU patients. This is a very appropriate approach to determining the place of nHF in a previously unstudied population of neonates - ie. those born and cared for in non-tertiary NICUs. This study has been funded and a good number of patients already enroled. As such, comments on the protocol at this stage cannot be used to amend the protocol and will only serve to determine the overall strength of the study and provide suggestions for clarification or additional analysis. In general, this is an excellent study designed and executed by a seasoned, productive research team. This group has played an important role in determining the efficacy and utility of nHF in the NICU and this study expands on their previous work by addressing another important clinical question - should nHF be used as a primary mode of respiratory support in non-tertiary NICUs? Infants cared for in these centres are more mature and robust than the more immature infants cared for in tertiary centers but many still exhibit varying degrees of respiratory distress and require some type of support. Of these, many suffer from minor transitional problems and

	settle quickly but a few can progress to more severe respiratory failure and require escalating levels of support and in many cases, transfer to the local regional tertiary NICU. As the investigators state, the type of respiratory support provided at presentation may influence the evolution of the respiratory condition, complication rates, subsequent disposition, resource utilization and costs. The background, methods, proposed analysis and discussion are well-written and appropriate. I have only a few minor comments for the investigators to consider as this study moves towards completion and publication. 1. The investigators use the acronym SCN for Special Care Nursery throughout to refer to the type of unit targeted for this study. This is not a term used in many other parts of the world to distinguish community-based, lower level NICUs from their tertiary counterparts. I would suggest that they describe the characteristics of their SCNs more thoroughly and relate them to the AAP levels of care designations (Specialty Care, Level 2). 2. Background, Page 5 - second paragraph. The investigators state that one of the reasons for pursuing an alternative method of respiratory support to nCPAP is that "CPAP may not be a feasible therapy in smaller SCNs". As per the above point on levels of care, Specialty Care, Level 2 units as per AAP should all have the capability of treating with CPAP. I suggest this piece of rationale be deleted. 3. Methods, Page 7 - Primary Outcome. I agree that objective criteria for failure need to be embedded in the study protocol but I wonder if the investigators could expand on one aspect of the criteria listed. This relates to how to manage babies with evolving RDS. Criteria for administration of surfactant to babies initially managed on nCPAP are controversial but many would say that they should receive surfactant if FIO2 reaches 0.4 (eg. European Consensus Guidelines, Neonatology 2017). What is the normal practice regarding surfactant treatment of babies with RDS initially managed with nCPAP in the participating centres? Does surfactant treatment mandate intubation? Does it mandate transfer? Does anyone do the INSURE or MIST procedure and keep the baby at the SCN? In the Clinical Management section, it is stated that, "surfactant may be administered at the paediatrician's discretion according to the unit's individual policy." I think it would be helpful for the reader to know what the usual practice is. This could go in the introduction or discussion section. 4. Page 8, Methods - Eligibility Criteria. It appears that babies are eligible if they require CPAP or supplemental oxygen for greater than an hour. How is it decided that a baby REQUIRES non-invasive respiratory support? Many neonates in the study population will exhibit some signs of respiratory distress such as grunting, indrawing or tachypnoea but many, especially those born by Caesarean section, have TTN/wet lung and are just slow to transition. The practice of placing such babies on CPAP has crept in with no real evidence that it speeds recovery and the vast majority of these babies will settle on their own within an hour or two. Did the investigators consider excluding babies on non-invasive support in room air? 5. Page 8, Methods - Eligibility Criteria. Is a CXR mandated before

	randomization? Since pneumothorax is considered one of the SAEs and spontaneous or early pneumothoraces are not uncommon in this population, I would hope that a CXR is done before randomization to rule it out. Page 11, Methods - Statistical analysis and economic evaluation plan. For the cost-effectiveness analysis described here, costs of patient transfer are not mentioned. This section should be aligned with Secondary Outcome #1. It would also be helpful to see more detail about how costs will be estimated. Page 12, Ethics and Dissemination - Monitoring and Safety. The acronym SAE usually refers to the term "Serious Adverse Event" which has a clear definition in clinical trial reporting. It is fair to say that pneumothorax and death would be considered Serious Adverse Events but other things may as well (such as if a study baby developed an infection)". Some use the term "SAE of interest" to define a particular subset of Serious Adverse Events that are most likely to be related to participation in the trial. 13. Page 13, Discussion - first paragraph. In the last line of the this paragraph, they state that "surfactant treatment, an intervention which may not be feasible in SCNs, and has not been shown to provide an advantage over routine CPAP treatment". This statement needs to be amended as it is only routine or prophylactic surfactant treatment that has not be shown to be superior to a CPAP first approach (that always includes selective surfactant treatment for those babies with significant RDS). So, placing a baby with early signs of respiratory distress on nHF or nCPAP will not eliminate RDS or the need for surfactant. It may allow babies who have no or very mild surfactant deficiency to escape more invasive treatments.

REVIEWER	Colm O'Donnell National Maternity Hospital; University College Dublin; National Children's Research Centre; all Dublin, Ireland
REVIEW RETURNED	28-Mar-2017

GENERAL COMMENTS	The authors describe a randomised non-inferiority trial comparing nasal high flow (nHF) therapy to nasal continuous positive airway pressure (CPAP) for the treatment of newly-born infants > 30 weeks' gestation with respiratory distress at non-tertiary special care nurseries in Australia. The authors are experienced and have an enviable track record in performing high-quality trials in this area. This is a novel, important and clinically relevant study that will have major implications for perinatal care in Australia and around the world. The economic evaluation of the trial will be important and fascinating. I commend them on their efforts, wish them well with their study and await the results with interest.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

We thank Dr Dunn for his excellent review and supportive comments.

Query:
The investigators use the acronym SCN for Special Care Nursery throughout to refer to the type of unit targeted for this study. This is not a term used in many other parts of the world to distinguish community-based, lower level NICUs from their tertiary counterparts. I would suggest that they describe the characteristics of their SCNs more thoroughly and relate them to the AAP levels of care designations (Specialty Care, Level 2).

Response:
Thank you. We feel that 'non-tertiary SCN' is a recognisable term for a Special Care Nursery that is not a NICU, indeed the AAP guidelines use the term 'Special Care Nursery' to describe level II neonatal centres. In Australia, non-tertiary hospitals that care for newborn infants range from AAP Level I to Level IIB equivalent, but with some inter-centre variation in practice and capabilities. Participating centres in our trial are either AAP level IIA or IIB equivalent: all would provide CPAP within local guidelines, but none would provide mechanical ventilation support, other than whilst awaiting transfer to a tertiary level NICU. In addition, smaller units (Level I-IIA equivalent) are increasingly keen to attempt short-term non-invasive support, but lack the caseload to effectively manage/practice CPAP. Nasal HF may well be useful in these centres should it be non-inferior to CPAP.

Australia also uses a system to classify Neonatal Unit capability however these differ between states and are not always interpreted correctly. Given the potential for confusion we think it best to avoid using any country or region-specific definition, but instead will provide the reader with more information so that they may better be able to relate the level of care provided at the participating centres with their own units.

We have made the following changes (bolded):
Background:
• "It is estimated that 2.5-5% of all newborn infants have respiratory distress.3 In Australia, most of these infants are born in a non-tertiary hospital and cared for in a special care nursery (SCN), where (depending on the level of neonatal care available) they may be treated with supplemental oxygen and/or 'non-invasive' respiratory support from nasal continuous positive airway pressure (CPAP). However, if these treatments are not available such as in some smaller SCNs, or not successful, or if an infant is born very preterm (<32 weeks' gestation) or very small (<1250 g), then the infant usually needs to be transferred to a tertiary-level neonatal intensive care unit (NICU). In Australia, neonatal intensive care is centralised in large metropolitan centres, and maternal and infant transfers from regional or rural centres involve large distances and significant costs."
• "CPAP is a widely-used method of respiratory support in larger Australian SCNs,8,9 but has some disadvantages. CPAP fixation devices are bulky and cover much of the infant's face, interfering with parental interaction and feeding; trauma to the nasal skin or septum is a commonly reported complication.10 Nursing vigilance is required to ensure that an adequate seal (and hence pressure) is maintained without causing nasal injury. For these reasons, and others including limits on staff and equipment, CPAP is not currently a feasible therapy in smaller Australian SCNs (with birth rates mostly <1500/year) that infrequently care for infants who require respiratory support."
Methods (Setting):
"The trial has been enrolling infants in nine non-tertiary SCNs in Victoria and New South Wales, Australia. All participating SCNs routinely care for newborn infants with respiratory distress, using CPAP as the standard non-invasive support mode; participating centres did not previously use nHF to treat newborn infants. No Australian SCNs provide ongoing mechanical ventilation; this is only provided whilst awaiting transfer of the infant to a tertiary NICU. Most participating centres administer exogenous surfactant if the infant requires intubation for RDS prior to retrieval by the neonatal transport team; the standard of care is that all of these infants are transferred to a tertiary NICU. Two

participating centres have some experience using the 'INSURE' (Intubate, Surfactant, Extubate) procedure [Ref: Isayama et al] in select infants with the support of the neonatal transport service (after which NICU transfer could potentially be avoided), but this is an infrequent practice that is staff-dependent. The participating SCNs have 24-hour on-site junior paediatric staff, and a designated on-call consultant paediatrician available to advise management and/or attend as required. Some participating centres have one or two consultant staff with specialist neonatal training, but most Australian SCNs do not."

Query:
Background, Page 5 - second paragraph. The investigators state that one of the reasons for pursuing an alternative method of respiratory support to nCPAP is that "CPAP may not be a feasible therapy in smaller SCNs". As per the above point on levels of care, Specialty Care, Level 2 units as per AAP should all have the capability of treating with CPAP. I suggest this piece of rationale be deleted.

Response:
We feel that the clarifications we have made above address this point.

Query:
Methods, Page 7 - Criteria for administration of surfactant to babies initially managed on nCPAP are controversial but many would say that they should receive surfactant if FIO2 reaches 0.4 (eg. European Consensus Guidelines, Neonatology 2017). What is the normal practice regarding surfactant treatment of babies with RDS initially managed with nCPAP in the participating centres? Does surfactant treatment mandate intubation? Does it mandate transfer? Does anyone do the INSURE or MIST procedure and keep the baby at the SCN? In the Clinical Management section, it is stated that, "surfactant may be administered at the paediatrician's discretion according to the unit's individual policy." I think it would be helpful for the reader to know what the usual practice is. This could go in the introduction or discussion section.

Response:
We think the above changes clarify this.

Query:
Page 8, Methods - Eligibility Criteria. It appears that babies are eligible if they require CPAP or supplemental oxygen for greater than an hour. How is it decided that a baby REQUIRES non-invasive respiratory support? Many neonates in the study population will exhibit some signs of respiratory distress such as grunting, indrawing or tachypnoea but many, especially those born by Caesarean section, have TTN/wet lung and are just slow to transition. The practice of placing such babies on CPAP has crept in with no real evidence that it speeds recovery and the vast majority of these babies will settle on their own within an hour or two. Did the investigators consider excluding babies on non-invasive support in room air?

Response:
We agree with the reviewer that there is a difference between "requires" and "receives". We tackle this issue by ongoing education of participating centres. As all participating centres have been using CPAP for many years and therefore making clinical decisions regarding the need for respiratory support, and because the HUNTER trial is a pragmatic one, we continue to leave the decision regarding the "need" for non-invasive respiratory support and therefore eligibility for randomisation with the treating clinician. We will be interested to explore this issue further once the trial is complete.

In the meantime, we have added the words "at clinician discretion" to the relevant eligibility criteria (#3). We have also added a paragraph to the discussion that addresses the pragmatic design of HUNTER: "The HUNTER trial is a pragmatic trial, designed to assess whether nHF is non-inferior to

CPAP in real-world practice. We have not mandated the need or timing of investigations such as chest x-rays or blood gas analysis, nor have we protocolised the decision to treat infants with non-invasive support, which remains at clinician discretion. We acknowledge that some randomised infants may have recovered from respiratory distress without the use of non-invasive support, or may have an unrecognised pneumothorax if randomised prior to a chest x-ray being performed."

Query:
Page 8, Methods - Eligibility Criteria. Is a CXR mandated before randomization? Since pneumothorax is considered one of the SAEs and spontaneous or early pneumothoraces are not uncommon in this population, I would hope that a CXR is done before randomization to rule it out.

Response:
No, a CXR is NOT mandated prior to randomisation. Again, in keeping with the pragmatic design of the study, and the aim to answer the question of whether HF may be used in place of CPAP, the timing of CXR is left to physician discretion. We agree pneumothoraces are not uncommon, and it is often unclear whether a pneumothorax was present prior to commencing CPAP or not (i.e. whether the respiratory distress being treated is secondary to a pneumothorax, or if it evolved later). Regardless, we did not want to exclude infants with pneumothoraces from the trial, as these patients will be managed in the SCN unless their respiratory distress worsens or they require drainage of the pneumothorax. As noted above, we have added a paragraph on the pragmatic nature of the study to the Discussion. To Clinical Management we have added "Chest X-rays and blood gas analyses are not mandated prior to randomisation, and the timing of these investigations will be at physician discretion in keeping with the pragmatic trial design, however it is expected that most enrolled infants will have these investigations performed as per local guidelines."

Query:
Page 11, Methods - Statistical analysis and economic evaluation plan. For the cost-effectiveness analysis described here, costs of patient transfer are not mentioned. This section should be aligned with Secondary Outcome #1. It would also be helpful to see more detail about how costs will be estimated.

Response:
The paragraph has been re-written as follows (changes in bold): "Cost-effectiveness analysis will be conducted from the healthcare system perspective, incorporating the costs of inpatient stay including the associated device and patient transfer costs. Routinely available costs of inpatient stay will be sourced from the hospital costing units. To inform whether it is cost-effective to incorporate nHF or CPAP into the existing health system, decision analysis will be constructed based on the primary outcome and associated hospital costs. Univariate and probabilistic sensitivity analyses will be conducted to test the impact of uncertainty in data."

Query:
Page 12, Ethics and Dissemination - Monitoring and Safety. The acronym SAE usually refers to the term "Serious Adverse Event" which has a clear definition in clinical trial reporting. It is fair to say that pneumothorax and death would be considered Serious Adverse Events but other things may as well (such as if a study baby developed an infection)". Some use the term "SAE of interest" to define a particular subset of Serious Adverse Events that are most likely to be related to participation in the trial.

Response:
Thank you, we have changed to 'Serious Adverse Event' as suggested. We acknowledge that other outcomes may be considered as adverse events. We have clarified in the text that the defined SAEs (pneumothorax and death) are those that in all cases will be reported to the relevant ethics

committees in this trial: “All incidences of these SAEs are reported to the lead Human Research Ethics Committee and to committees at the relevant site.”

Query:
13. Page 13, Discussion - first paragraph. In the last line of the this paragraph, they state that "surfactant treatment, an intervention which may not be feasible in SCNs, and has not been shown to provide an advantage over routine CPAP treatment". This statement needs to be amended as it is only routine or prophylactic surfactant treatment that has not be shown to be superior to a CPAP first approach (that always includes selective surfactant treatment for those babies with significant RDS). So, placing a baby with early signs of respiratory distress on nHF or nCPAP will not eliminate RDS or the need for surfactant. It may allow babies who have no or very mild surfactant deficiency to escape more invasive treatments.

Response:
Thank you for your suggestion. We have amended this section to read: “The other recently published trial of primary nHF was also performed in a NICU, and included a high rate of surfactant administration by the INSURE technique, an intervention which is not currently practiced routinely in Australian SCNs, and that has not been well-studied in the SCN setting or in the infant population relevant to SCNs (infants ≥31 weeks’ GA).”

Reviewer 2

We thank Dr O’Donnell for his kind words. He had no queries.

Other minor changes

1. Acknowledgements: Added “Health Economics: Li Huang, The University of Melbourne.”

2. Study design:

a. Added the word ‘Australian’: “HUNTER is a multicentre, randomised, non-inferiority trial, including newborn infants cared for in Australian non-tertiary SCNs.”

b. Added reference to the FIGURE: “A schedule of enrolment, interventions, and assessments is shown in the FIGURE.”

3. Current status and study duration: Added “To the end of March 2017, over 500 infants have been enrolled in the trial.”

4. References: Minor corrections to where some citations were used, and to formatting of the bibliography.

5. Added a Figure Legend after the references: ”FIGURE. Schedule of enrolment, interventions, and assessments: The HUNTER Trial.”

VERSION 2 – REVIEW

REVIEWER	Michael Dunn Sunnybrook Health Sciences Centre Toronto, Ontario CANADA
REVIEW RETURNED	28-Apr-2017

GENERAL COMMENTS	I believe that Dr. Manley and coauthors have effectively addressed my concerns. I look forward to seeing the results of this excellent study.