PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A multicentre, randomised trial of stabilisation with nasal high flow during neonatal endotracheal intubation (the SHINE trial): a study protocol
AUTHORS	Hodgson, Kate A; Owen, Louise S; Kamlin, Camille Omar; Roberts, Calum T; Donath, Susan M; Davis, Peter G.; Manley, Brett James

VERSION 1 – REVIEW

REVIEWER	Eugene Dempsey University College Cork Ireland
REVIEW RETURNED	10-May-2020

GENERAL COMMENTS	Thank you for asking me to review this protocol. It addresses a very important area of newborn care, and any intervention that may improve success rates and at the same time decrease physiological instability associated with the procedure is very welcome. The protocol is clearly presented. I have only a few comments outlined below. Introduction The authors introduce the concept of THRIVE. For many neonatologists this will not be something they are familiar with and further explanation, including apneic oxygenation and cardiac oscillations is warranted. Also the data presented relates to trials in children and adults. How does the delivery differ in THRIVE eg flow rates ? , compared to nasal HF in neonates? Or does it differ? Methods Sample size estimate. I think 30 % is a reasonable percentage to assume. However this may be an underestimate/overestimate considering previous work this group carried out , eg when evaluating the use of a stylet or not during intubation. The success rates on this occasion were in the high 50's, although I do not think the desaturation/bradycardia is reported. In the O'Shea paper the success rate was 66% versus 60% for the video versus standard group, albeit the percentage of destaration/bradycardia will reduce this but I am not certain if this percentage was more marked in the non-video group. The overall success rate and its variability should be discussed as a potential limitation. Intervention groups NHF group. One of the potential biases is the issue around preoxygenation, which will eb at the discretion of the clinical team.

	Will the FiO2 concentration, and the duration of time from application of the NHF be recorded for each baby? I think this should be recorded as some objective way of recording the potential oxygen load that each infant is exposed to? Secondary Outcomes. Was any consideration given to the duration of time the saturation values may have been above a certain valueeg 97% or some other measure of potential oxygen toxicity?

REVIEWER	Jane PillowNone The University of Western Australia
REVIEW RETURNED	24-May-2020

GENERAL COMMENTS	The manuscript outlines the protocol for a multicentre randomised controlled trial that appears to have already commenced recruitment. Overall, the protocol is written well and adheres to the SPIRIT guidelines. Blinding is not practical for this short term trial, due to the nature of the intervention, and its presence being apparent to the investigator noting physiological responses - the only way around this would be to .record physiological data without resorting to use of a video recording, and having those data analysed by an investigator blinded to the randomisation. The authors could improve the manuscript marginally by: - replacing passive tense with active verbs - bringing the subject of the sentence to the front of the sentence, rather than placing it in the middle or at the end following a number of restrictive clauses which are more logically placed after the verb - clarifying why the protocol/individual level patient datasets/statistical code will not be made available to the public

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Thank you for asking me to review this protocol. It addresses a very important area of newborn care, and any intervention that may improve success rates and at the same time decrease physiological instability associated with the procedure is very welcome. The protocol is clearly presented. I have only a few comments outlined below.

Thank you for your supportive comments.

Introduction
The authors introduce the concept of THRIVE. For many neonatologists this will not be something they are familiar with and further explanation, including apneic oxygenation and cardiac oscillations is warranted. Also the data presented relates to trials in children and adults. How does the delivery differ in THRIVE eg flow rates ? , compared to nasal HF in neonates? Or does it differ?

Thank you for this suggestion. The Introduction section has been expanded to include further explanation of the physiological concepts underpinning apnoeic oxygenation and THRIVE (page 4 lines 19-34 and page 5 lines 3-8). Further details including flow rates in the two published paediatric randomised trials have been included (page 5 lines 13-15 and20-30). There are no specific neonatal data regarding THRIVE.

Methods
Sample size estimate. I think 30 % is a reasonable percentage to assume. However this may be an underestimate/overestimate considering previous work this group carried out ,eg when evaluating the

use of a stylet or not during intubation. The success rates on this occasion were in the high 50's, although I do not think the desaturation/bradycardia is reported. In the O'Shea paper the success rate was 66% versus 60% for the video versus standard group, albeit the percentage of destaration/bradycardia will reduce this but I am not certain if this percentage was more marked in the non-video group. The overall success rate and its variability should be discussed as a potential limitation.

> Thank you for this comment. This sample size estimate is for the combined primary outcome of successful intubation without physiological instability (desaturation or bradycardia). We acknowledge that there is indeed variation in success rates during neonatal intubation. The sample size estimate was determined from the O'Shea et al. data including both video and non-video laryngoscope intubations, given that this reflects practice in the centres recruiting patients in this study. Further discussion regarding the uncertainty and variability of success rates for neonatal intubation has been added to the Sample Size section as suggested. Please see page 6 lines 24-27.

Intervention groups
NHF group. One of the potential biases is the issue around preoxygenation, which will eb at the discretion of the clinical team.

> Thank you for this comment. Both the starting FiO_2 immediately prior to laryngoscopy(equal to that the baby was previously receiving, at clinician discretion), as well as the starting SpO_2 are recorded on the Case Report Form, in order to evaluate any bias with respect to preoxygenation between the groups.

Will the FiO2 concentration, and the duration of time from application of the NHF be recorded for each baby? I think this should be recorded as some objective way of recording the potential oxygen load that each infant is exposed to?

> The starting FiO_2 of the nHF and the maximum FiO_2 delivered by the nHF during the intubation attempt are both recorded. The duration of time the nHF prongs are in situ is also available from the video review, therefore these two indicators of potential oxygen load could be reported for the intervention group.

Secondary Outcomes.
Was any consideration given to the duration of time the saturation values may have been above a certain valueeg 97% or some other measure of potential oxygen toxicity?

> Thank you for this suggestion. Currently, $SpO_2$and heart rate are recorded at 2-second intervals during the intubation attempt from the oximeteror video.The median SpO_2 for the duration of laryngoscopy and attempted intubation is recorded for each patient.We have added median SpO_2, as well as duration with SpO_2>97% as secondary outcomes within the protocol manuscript, as a measure of potential oxygen toxicity due to nHF (page 9 lines 26-28). Some babies in the intervention group may receive no oxygen during the intubation attempt (if they were not receiving oxygen prior, at clinician discretion, and their SpO_2 remains >90%), therefore the most accurate comparison of high SpO_2between the groups will exclude these babies.

Reviewer: 2
The manuscript outlines the protocol for a multicentre randomised controlled trial that appears to have already commenced recruitment. Overall, the protocol is written well and adheres to the SPIRIT guidelines. Blinding is not practical for this short term trial, due to the nature of the intervention, and its

presence being apparent to the investigator noting physiological responses - the only way around this would be to .record physiological data without resorting to use of a video recording, and having those data analysed by an investigator blinded to the randomisation.

> Thank you for this comment. Whilst the investigators will not be blinded to the intervention during the video review, in an attempt to minimise bias a second investigator will verify the primary outcome and any discrepancies will be resolved by a third assessor from the Trial Steering Committee.

The authors could improve the manuscript marginally by:
- replacing passive tense with active verbs
- bringing the subject of the sentence to the front of the sentence, rather than placing it in the middle or at the end following a number of restrictive clauses which are more logically placed after the verb

> We have edited some sections of the manuscript to reflect these suggestions. Please see page8 lines 4, 5 and 15and page 11 lines 15-21.

- clarifying why the protocol/individual level patient datasets/statistical code will not be made available to the public

The protocol will be published and publicly available. Deidentified individual level patient datasets and statistical code will be made available upon reasonable request. This has been corrected in the SPIRIT guideline checklist and clarified in the manuscript. Please see page 2 lines 4-6.

VERSION 2 – REVIEW

REVIEWER	Eugene Dempsey INFANT Centre, Cork University Maternity Hospital Cork Ireland
REVIEW RETURNED	05-Aug-2020

GENERAL COMMENTS	The authors have adequately addressed all my comments.