PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Incremental Effect of Non-Invasive Oscillating Device on Chest Physiotherapy in Critically Ill Children: A Cross-Over Randomized Trial
AUTHORS	Kawaguchi, Atsushi; Bernier, Gabrielle; Adler, Andy; Emeriaud, Guillaume; Jouvet, Philippe A.

VERSION 1 – REVIEW

REVIEWER	Colum Dunne School of Medicine University of Limerick Ireland Inventor of an oscillating positive expiratory pressure (OPEP) respiratory medical device
REVIEW RETURNED	14-May-2020

GENERAL COMMENTS	The challenge of studying respiratory parameters in young children is evident in this protocol. The authors present a clearly-stated rationale. However, three items could usefully receive some additional attention: a) some language editing would improve clarity in describing the intended work. This is not a major item, but would improve the text and permit better understanding of some aspects. b) the protocol states that there is a lack of literature regarding the NIOD and the specific device. Therefore, additional information on both is needed to allow a reader understand the mechanisms involved and the characteristics of the device involved.This is a major item. c) the title states that this is a randomised, controlled study. In reality, while there is some randomisation across limbs, the protocol is not controlled as each child will receive NIOD. In addition, each child will also receive standard of care physiotherapy. In that sense, any effect of NIOD is incremental and, as such, the protocol is testing physiotherapy plus NIOD and not any isolated NIOD. That fact is not clear in the protocol and analysis of outcomes should be interpreted in that context. This is a major item.

REVIEWER	Lisa Morrison West of Scotland Adult CF Unit Queen Elizabeth University Hospital 1345 Govan Road Glasgow G51 4Tf UK
REVIEW RETURNED	27-May-2020

GENERAL COMMENTS	I believe that the NIOD perhaps has not been clearly explained I am unclear as to how this device actually works or indeed what it looks like, the space it will take up on the chest wall and specifically how this will influence the secretions. I am aware that oscillation will affect viscoelasticity of secretions but is this how the NIOD is proposed to work and if so please can this be mentioned. I am a little concerned re the chest "striking" as this is not how CPT was described in the initial introduction. I wonder about the use of Lung clearance index as an outcome measure as this has a greater recognition of clinical importance and is perhaps a more useful and transferable outcome measure. I believe the COMFORT scale needs to be explained as I am unfamiliar with this scale. I am concerned that Stage 2 has both CPT and NIOD in the intervention. I think that there is a possibility that this will confound the results and as will not be aware of any carry over effects of either the NIOD or CPT in stage 2 and this will influence the possible results and benefits experienced by one or other of the interventions.

REVIEWER	Maria Kompoti Intensive Care Unit, Thriassio General Hospital of Eleusis, Athens, Greece
REVIEW RETURNED	26-Jun-2020

GENERAL COMMENTS	This is a well-designed protocol of a cross-over RCT. However, a crucial concern arises regarding randomization process. The exclusion of patients based on the physician's "expectation" that CPT will be discontinued within 24h generates a source of randomization bias. Exclusion criteria should involve characteristics present at randomization and not expected to evolve in a later time point. The authors shoud define robust exclusion criteria not subjected to participation or researcher's bias.

VERSION 1 – AUTHOR RESPONSE

Comments from Reviewers
Responses to Reviewer's Comments:

Reviewer: 1
(1) three items could usefully receive some additional attention: some language editing would improve clarity in describing the intended work. This is not a major item, but would improve the text and permit better understanding of some aspects.

[Response] Thank you for this feedback. According this, we have proofread the manuscript again and revised as needed.

(2) the protocol states that there is a lack of literature regarding the NIOD and the specific device. Therefore, additional information on both is needed to allow a reader understand the mechanisms involved and the characteristics of the device involved.

[Response] We agree this point. We have added a supplemental document presenting the detailed mechanism of the NIOD.

(3) the title states that this is a randomised, controlled study. In reality, while there is some randomisation across limbs, the protocol is not controlled as each child will receive NIOD. In addition, each child will also receive standard of care physiotherapy. In that sense, any effect of NIOD is incremental and, as such, the protocol is testing physiotherapy plus NIOD and not any isolated NIOD. That fact is not clear in the protocol and analysis of outcomes should be interpreted in that context. This is a major item.

[Response] We agree with thisnpoint. According to the feedback, we have changed the title to “Incremental Effect of Non-Invasive Oscillating Device on Chest Physiotherapy in Critically Ill Children: A Cross-Over Randomized Trial”. Also, in the method section, we have added a sentence “We will compare the two groups (1. CPT Only and 2. CPT with NIOD) for the following outcome items.” To clarify the comparisons and its aims.

Reviewer: 2

(1) I believe that the NIOD perhaps has not been clearly explained I am unclear as to how this device actually works or indeed what it looks like, the space it will take up on the chest wall and specifically how this will influence the secretions. I am aware that oscillation will affect viscoelasticity of secretions but is this how the NIOD is proposed to work and if so please can this be mentioned. I am a little concerned re the chest "striking" as this is not how CPT was described in the initial introduction.

[Response] Thank you for this feedback. According to the feedback, we have added a supplemental document presenting the detailed mechanism of NIOD.

(2) I wonder about the use of Lung clearance index as an outcome measure as this has a greater recognition of clinical importance and is perhaps a more useful and transferable outcome measure. I believe the COMFORT scale needs to be explained as I am unfamiliar with this scale.

[Response] Thank you for pointing this out. Based on this, we have added a sentence as “Primary Outcome: Mean modified COMFORT scale two minutes from the initiation of the procedure (15, 16), which is a behavioral, unobtrusive method of measuring distress in unconscious and ventilated infants, children and adolescents using eight different indicators.” on pp10.

(3) I am concerned that Stage 2 has both CPT and NIOD in the intervention. I think that there is a possibility that this will confound the results and as will not be aware of any carry over effects of either the NIOD or CPT in stage 2 and this will influence the possible results and benefits experienced by one or other of the interventions.

[Response] we understand this potential carry-over effect. That’s the main passion why we designed randomized allocation of the cohorts. Moreover, although the evidence does not support thoroughly the routine CPT for the critically ill children, it is one of the standard ICU cares in our daily practice; therefore, we believe it is not ethically appropriate to set a control group without CPT in the care.

Reviewer: 3

(1) The exclusion of patients based on the physician's "expectation" that CPT will be discontinued within 24h generates a source of randomization bias. Exclusion criteria should involve characteristics

present at randomization and not expected to evolve in a later time point. The authors should define robust exclusion criteria not subjected to participation or researcher's bias.

[Response] Thank you for the feedback. The person who will perform the patient screening will be different from the person who will order CPT; therefore, we think the randomization bias should not be an major concern in our design. We also, think CPT should not be performed when clinicians think it does not need to be done.

VERSION 2 – REVIEW

REVIEWER	Colum Dunne University of Limerick, Ireland
REVIEW RETURNED	25-Jul-2020

GENERAL COMMENTS	The Revised manuscript has dealt with previous comments.

REVIEWER	Lisa Morrison West of Scotland Adult CF Unit Queen Elizabeth University Hospital 1345 Govan Road Glasgow G51 4TF UK
REVIEW RETURNED	24-Jul-2020

GENERAL COMMENTS	I am still uncomfortable with the phrase "CPT will be defined as an assistant strike to the chest wall repeatedly with a cupped hand in specific places." I believe this should be changed to "CPT will be standardised to include manual techniques of percussion (with a cupped hand) and vibrations for a set period of time over the chest wall" Thank you for addressing the other issues previously highlighted