PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	REVISE: Re-Evaluating the Inhibition of Stress Erosions in the ICU: A Randomized Trial Protocol
AUTHORS	Deane, Adam M; Alhazzani, Waleed; Guyatt, Gordon; Finfer, Simon; Marshall, John; Myburgh, John; Zytaruk, Nicole; Hardie, Miranda; Saunders, Lois; Knowles, Serena; Lauzier, Francois; Chapman, Marianne J.; English, Shane; Muscedere, John; Arabi, Yaseen; Ostermann, Marlies; Venkatesh, Balasubramanian; Young, Paul; Thabane, Lehana; Billot, Laurent; Heels-Ansdell, Diane; Al-Fares, Abdulrahman A; Hammond, Naomi; Hall, R.; Rajbhandari, Dorrilyn; Poole, Alexis; Johnson, Daniel; Iqbal, Mobeen; Reis, Gilmar; Xie, Feng; Cook, Deborah; * Deane and Alhazzani are co-first authors, for the CCCTG & ANZICS-CTG

VERSION 1 – REVIEW

REVIEWER	Skurzak, Stefano Ospedale San Giovanni Battista, Dipartimento di Anestesia e di Medicina degli Stati Critici
REVIEW RETURNED	30-Jul-2023

GENERAL COMMENTS	I am honored to have the opportunity of reviewing a study protocol realized by an international group of top trialists. The study protocol is extremely accurate and complete, I have few major observations arising from my clinical practice: ENTERAL NUTRITION The authors affirm that: “Patients not receiving invasive mechanical ventilation are excluded and most eligible patients will receive enteral nutrition; trial results may have limited applicability to fasting patients and those receiving parenteral nutrition or non-invasive ventilation.” and that: “REVISE will not provide direct evidence about pantoprazole’s effect on patients requiring non-invasive ventilation or no support, or patients without enteral nutrition.” Fasting and/or total parenteral nutrition are not an exclusion criteria for the REVISE study. Even if the prevalence of these patients is expected to be rather low, the above mentioned sentences are inappropriate in a study protocol publication. Subgroup analysis for

	this high risk group should be instead preplanned. CONSENT, WITHDRAWAL OF CONSENT, PHYSICIAN DECLINE, DISCONTINUATION, UNBLINDING FOR EMERGENCY The authors reported that: “Patients and families will be involved in several ways. We completed two pilot trials, documenting consent rates of 98.1% [11] and 77.8% [12].” (a 20% difference!) and that: “...enrolled patients who regain capacity after critical illness are notified about the trial and approached for consent...” I strongly believe that important Trial as REVISE should document all these aspects with complete reports on consent rates overall and per center, retired consents, discontinuation/protocol violation, unblinding for emergency. I suppose that physician decline to enroll a patient is a more difficult information to obtain but it would be useful too. The study protocol should affirm that all these cases will be reported in the main publication of study results. DATA COLLECTED The description on which data are collected is too much concise (“Following protocol training, research staff collect baseline data (e.g., illness severity, comorbidities), daily data up to 90 days post-randomization (e.g., advanced life support), laboratory values (e.g., hemoglobin, INR, platelet count); cointerventions (e.g., enteral nutrition, anticoagulants)...”). Complete Case Report Form should be attached as supplementary material to the study protocol. PREPLANNED SUBGROUP ANALYSIS AND RISK FOR GASTROINTESTINAL BLEEDING The authors refer to the article by Ye Z, Reintam Blaser A, Lytvyn L, Wang Y, Guyatt GH, Mikita JS, Roberts J, Agoritsas T, Bertschy S, Boroli F, Camsooksai J, Du B, Heen AF, Lu J, Mella JM, Vandvik PO, Wise R, Zheng Y, Liu L, Siemieniuk RAC. Gastrointestinal bleeding prophylaxis for critically ill patients: a clinical practice guideline. BMJ. 2020 Jan 6;368:l6722. doi: 10.1136/bmj.l6722. PMID: 31907223 which describe 4 categories of risk for gastrointestinal bleeding based on a previous metanalysis (Granholm A, Zeng L, Dionne JC, Perner A, Marker S, Krag M, MacLaren R, Ye Z, Møller MH, Alhazzani W; GUIDE Group. Predictors of gastrointestinal bleeding in adult ICU patients: a systematic review and meta-analysis. Intensive Care Med. 2019 Oct;45(10):1347-1359. doi: 10.1007/s00134-019-05751-6. Epub 2019 Sep 5. PMID: 31489445.). I understand that the REVISE study was intended to cover the entire spectrum of risk for gastrointestinal bleeding but I would have expected a study design and sample size calculations (in terms of recruitable patients for different categories, especially after interim

	analysis) more centered on the risk categories (high vs low at least). I think that these two subgroups should be considered in the list of “a priori subgroup pairs” (“Subgroup analyses will be conducted for the primary efficacy outcome and primary safety outcome infive a priori subgroup pairs: 1) Pre-hospital acid suppression (PPIs or H2RAs) vs. none, 2) Illness severity per APACHE II score of >25 or <25, 3) 3) Medical vs. surgical/trauma ICU admitting diagnosis, 4) SARS-CoV-2 positive vs. negative status, and 5) Female vs. male.”) otherwise a discussion on this point would be useful beyond the expected future publications on predictors of gastrointestinal bleeding. Minor Observations: In the ClinicalTrial.gov site the study NCT03374800 contains a list of exclusion criteria different from the one here reported (in particular cirrhosis for Australia and Pregnancy), please clarify. In the proof the tables are duplicated. In the two copies of Legend for table 3 (the first being PAGE 18 LINES 48-50 “The table presents combinations of relative risks ranging from 1.1 to 1.3, and baseline risks between 38% and 4%,...”. The 4% should be corrected with 44%.

REVIEWER	Kazmi, Syed Sajid Hussain Oslo University Hospital, Department of Vascular Surgery
REVIEW RETURNED	05-Aug-2023

GENERAL COMMENTS	I am honored to review the study protocol for REVISE Trial. I congratulate the authors and their collaborators on planning such an exciting study. It clearly describes the study's background, rationale, and well-defined aims with relevant background references. They have presented all the measures taken to reduce the study bias and increase the study's internal and external validity in writing and table forms. Sample size calculations and the in priori appropriate statistical strategy have added to the strengths of this study. I have just noted a couple of issues that the authors can address. 1- The abstract should add that the study population is mechanically ventilated ICU patients with enteral nutrition. 2-Remove "of" in line 24 under the subheading Clinically Important GI Bleeding: or rephrase the sentence. 3-Although, under the section "Knowledge Translation," the authors have mentioned that REVISE will not provide direct evidence about pantoprazole's effect on MVP ICU patients without enteral nutrition, they should also add this information under the 'Status' section in paragraph 2 since the information in the paragraph may be wrongly interpreted as the effects of pantoprazole on all types of ICU patients. 4- Limited information about the funding has first come under the legends for Table 2; it should be written in the manuscript and should add some details about hybrid serial funding.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Stefano Skurzak, Ospedale San Giovanni Battista

I am honored to have the opportunity of reviewing a study protocol realized by an international group of top trialists. The study protocol is extremely accurate and complete, I have few major observations arising from my clinical practice:

** Thank you very much for your positive comments. We are grateful for your time.

ENTERAL NUTRITION
The authors affirm that:
"Patients not receiving invasive mechanical ventilation are excluded and most eligible patients will receive enteral nutrition; trial results may have limited applicability to fasting patients and those receiving parenteral nutrition or non-invasive ventilation."
and that:
"REVISE will not provide direct evidence about pantoprazole's effect on patients requiring non-invasive ventilation or no support, or patients without enteral nutrition."
Fasting and/or total parenteral nutrition are not an exclusion criteria for the REVISE study. Even if the prevalence of these patients is expected to be rather low, the above mentioned sentences are inappropriate in a study protocol publication. Subgroup analysis for this high risk group should be instead preplanned.

** We appreciate the chance to clarify. The reviewer is correct that patients who are fasting or nil per os, and/or receiving parenteral nutrition are not excluded from REVISE. However, we anticipate that, based on practice patterns, there will be few such patients. For this and other reasons (such as the fact that feeding status is not a baseline characteristic and can change over time during critical illness), this is not a suitable subgroup characteristic.o pre-planned subgroup analysis based on enteral nutrition. Our subgroup analyses were certainly pre-specified and we cannot change them post hoc. We have omitted this sentence. Thank you. The article Summary section is now simplified as follows to remove reference to enteral nutrition (and allow this to be explained in the Knowledge Translation section below):

- "Patients not receiving invasive mechanical ventilation are excluded; trial results may have limited applicability to spontaneously breathing patients and those receiving non-invasive ventilation"

** We have modified a sentence in the Knowledge Translation section, as follows:

"Given contemporary critical care practice, we anticipate that a small proportion of enrolled patients will receive no enteral nutrition, such that inferences about this population may be limited."

CONSENT, WITHDRAWAL OF CONSENT, PHYSICIAN DECLINE, DISCONTINUATION, UNBLINDING FOR EMERGENCY
The authors reported that: "Patients and families will be involved in several ways. We completed two pilot trials, documenting consent rates of 98.1% [11] and 77.8% [12]." (a 20% difference!)
and that:
"...enrolled patients who regain capacity after critical illness are notified about the trial and approached for consent..."
I strongly believe that important Trial as REVISE should document all these aspects with complete reports on consent rates overall and per center, retired consents, discontinuation/protocol violation, unblinding for emergency. I suppose that physician decline to enroll a patient is a more difficult

information to obtain but it would be useful too. The study protocol should affirm that all these cases will be reported in the main publication of study results.

** Thank you for these observations and great suggestions. In the main report, we will indicate informed consent rates (which includes 'retired consents' if that means consent declines), days of study drug exposure (central tendency and measure of dispersion), and protocol deviations (e.g., administration of open label proton pump inhibitor or histamine-2-receptor antagonist, missed doses of study drug, or dispensing the wrong study drug [e.g., pantoprazole given instead of placebo or vice versa]). We will indicate any need for unblinding (to date we can confirm that there have been no unblinding requests). These factors were also analyzed for the interim analysis, as indicated in the original submission under the Data Monitoring Committee section. Physician comfort or discomfort data are not collected. In response to these questions, we created a new section in the revised protocol manuscript labelled Trial Process Metrics. Thank you for this idea.

"Trial Process Metrics

We will report informed consent rates and coenrolment rates, and any need for unblinding.

In terms of protocol adherence, we will report days of study drug exposure and reasons for non-administration of study drug. Protocol deviations will include administration of open label proton pump inhibitor or histamine-2-receptor antagonist, missed doses of study drug, or dispensing the wrong study drug (e.g., pantoprazole given instead of placebo or vice versa)."

DATA COLLECTED

The description on which data are collected is too much concise ("Following protocol training, research staff collect baseline data (e.g., illness severity, comorbidities), daily data up to 90 days post-randomization (e.g., advanced life support), laboratory values (e.g., hemoglobin, INR, platelet count); cointerventions (e.g., enteral nutrition, anticoagulants)..."). Complete Case Report Form should be attached as supplementary material to the study protocol.

** The description of data collection is fully detailed in the Case Report Forms which are uploaded to form Supplemental Appendix 2. Thank you for this suggestion. We have embellished this part of the methods section a bit further as well, as follows:

"Data Collection

Research staff collect baseline data about the patients (e.g., illness severity, comorbidities, pre-hospital acid suppression), and daily data up to 90 days post-randomization while in the ICU. This includes advanced life supports received, key laboratory values (e.g., hemoglobin, INR, platelet count); cointerventions (e.g., enteral nutrition, anticoagulants, non-steroidal anti-inflammatory agents, corticosteroids), and relevant hospital reports (e.g., endoscopy, radiology, surgery). Research staff follow patients daily to document study drug receipt or reasons for non-administration, while tracking trial outcomes as listed below. The duration of mechanical ventilation, ICU and hospital stay, and mortality are documented. Patients discharged alive from hospital before 90 days are followed for 90 days; vital status is obtained by patient, family or family physician contact, regional obituary or health-record review. No biological specimens are collected. The case report forms with additional details are found in Supplemental Appendix 2."

PREPLANNED SUBGROUP ANALYSIS AND RISK FOR GASTROINTESTINAL BLEEDING

The authors refer to the article by Ye Z, Reintam Blaser A, Lytvyn L, Wang Y, Guyatt GH, Mikita JS, Roberts J, Agoritsas T, Bertschy S, Boroli F, Camsooksai J, Du B, Heen AF, Lu J, Mella JM, Vandvik PO, Wise R, Zheng Y, Liu L, Siemieniuk RAC. Gastrointestinal bleeding prophylaxis for critically ill patients: a clinical practice guideline. BMJ. 2020 Jan 6;368:l6722. doi: 10.1136/bmj.l6722. PMID: 31907223 which describe 4 categories of risk for gastrointestinal bleeding based on a previous metanalysis (Granholm A, Zeng L, Dionne JC, Perner A, Marker S, Krag M, MacLaren R, Ye Z, Møller MH, Alhazzani W; GUIDE Group. Predictors of gastrointestinal bleeding in adult ICU patients: a systematic review and meta-analysis. Intensive Care Med. 2019 Oct;45(10):1347-1359. doi: 10.1007/s00134-019-05751-6. Epub 2019 Sep 5. PMID: 31489445.).

I understand that the REVISE study was intended to cover the entire spectrum of risk for gastrointestinal bleeding but I would have expected a study design and sample size calculations (in terms of recruitable patients for different categories, especially after interim analysis) more centered on the risk categories (high vs low at least). I think that these two subgroups should be considered in the list of “a priori subgroup pairs” (“Subgroup analyses will be conducted for the primary efficacy outcome and primary safety outcome in five a priori subgroup pairs: 1) Pre-hospital acid suppression (PPIs or H2RAs) vs. none, 2) Illness severity per APACHE II score of >25 or <25, 3) 3) Medical vs. surgical/trauma ICU admitting diagnosis, 4) SARS-CoV-2 positive vs. negative status, and 5) Female vs. male.”) otherwise a discussion on this point would be useful beyond the expected future publications on predictors of gastrointestinal bleeding.

** The REVISE protocol was not designed to recruit a fixed number of patients in different risk categories; we sought to enrol a heterogeneous group of patients, who will be at variable risk for gastrointestinal bleeding, but all of whom require mechanical ventilation as a marker of illness severity. This design was adopted to enhance the generalizability of our findings within a population of critically ill patients needing the commonest form of advanced life support.

** The REVISE interim analysis was in November 2022. We have not analyzed how many patients are in each of the subgroup pair, but we will certainly include this information in the main report. One estimate we are happy to share now, given the state of the pandemic, is that there may be approximately 500 patients with COVID-19 and the remaining 4,300 patients without.

** The REVISE subgroup analyses were established a priori, after lengthy discussion and consensus amongst the International Management Committee, Canadian Steering Committee, Australian Steering Committee, the Canadian Critical Care Trials Group and Australian and New Zealand Intensive Care Society Clinical Trials Group. We are uncomfortable making post hoc changes to our analysis plan. Using regression analysis, we look forward to further understanding independent risk factors for bleeding in this invasively ventilated cohort.

Minor Observations:
In the ClinicalTrial.gov site the study NCT03374800 contains a list of exclusion criteria different from the one here reported (in particular cirrhosis for Australia and Pregnancy), please clarify.

** In Australia, patients with cirrhosis were excluded. They were not excluded in other parts of the world. We have added this information to the revised protocol, incorporated in the section about local contraindications in Australia.

- “Pantoprazole contraindication per local product information (in Australia: being treated with the human immunodeficiency virus protease inhibitors atazanavir or nelfinavir, being treated with high dose methotrexate (i.e. >300mg as part of a chemotherapy regimen), and documented cirrhosis or severe liver disease (e.g., as indicated by an international normalized ratio > 5.0 due to underlying liver disease); in Canada: being treated with rilpivirine or atazanavir, and patients who are hypersensitive to pantoprazole, substituted benzimidazoles, or to any ingredient in the formulation)”

** Pregnant patients were universally excluded from REVISE. This was indicated as a bullet in our protocol paper and has a separate category in our case report forms. We have now added this to the clinicaltrials.gov website. Thank you!

In the proof the tables are duplicated. In the two copies of Legend for table 3 (the first being PAGE 18 LINES 48-50 “The table presents combinations of relative risks ranging from 1.1 to 1.3, and baseline risks between 38% and 4%,...”. The 4% should be corrected with 44%.

** Sorry we uploaded two copies of Table 3. One is uploaded now. Thank you for pointing out the missing ‘4’ which is now corrected.

Best regards

** We appreciate your careful review and suggestions. We would like to include you in the Acknowledgements section of this article.

Reviewer: 2
Dr. Syed Sajid Hussain Kazmi, Oslo University Hospital, University of Oslo

Comments to the Author:
I am honored to review the study protocol for REVISE Trial.
I congratulate the authors and their collaborators on planning such an exciting study. It clearly describes the study's background, rationale, and well-defined aims with relevant background references.
They have presented all the measures taken to reduce the study bias and increase the study's internal and external validity in writing and table forms. Sample size calculations and the in priori appropriate statistical strategy have added to the strengths of this study.

** We appreciate your positive reflections on this protocol.

I have just noted a couple of issues that the authors can address.
1- The abstract should add that the study population is mechanically ventilated ICU patients with enteral nutrition.

** We have added again the word ‘mechanically’ to the description of the population so that this word is stated twice in this sentence of the abstract. Although most patients in REVISE will have enteral nutrition, this is not an inclusion criterion, so we did not add that to the abstract. Thank you for the chance to clarify.

“Patients ≥18 years old expected to remain invasively mechanically ventilated beyond the calendar day after enrolment are being randomized to either 40 mg pantoprazole intravenously or an identical placebo daily while mechanically ventilated in the ICU.”

2-Remove "of" in line 24 under the subheading Clinically Important GI Bleeding: or rephrase the sentence.

** We removed the word ‘of’ before clinically important bleeding and 90-day mortality, which we hope is what you mean.

3-Although, under the section "Knowledge Translation," the authors have mentioned that REVISE will not provide direct evidence about pantoprazole's effect on MVP ICU patients without enteral nutrition,

they should also add this information under the 'Status' section in paragraph 2 since the information in the paragraph may be wrongly interpreted as the effects of pantoprazole on all types of ICU patients.

** We appreciate the chance to clarify this issue. Some patients in REVISE will be receiving enteral nutrition, some will have no nutrition and some will have parenteral nutrition. Also, one patient may be in all three states over the course of their ICU stay, depending on their clinical condition. REVISE is not enrolling only patients who are receiving enteral nutrition (i.e., this is not an inclusion criterion); however, most patients will be receiving enteral nutrition unless contraindications exist, as per contemporary critical care medicine. This may be too confusing as the Reviewer suggests, so we have simplified the Summary Bullets and the fourth one now says:

- "Patients not receiving invasive mechanical ventilation are excluded; trial results may have limited applicability to spontaneously breathing patients or those receiving non-invasive ventilation"

** We have also updated the first paragraph of the Status section as follows:

"REVISE will not provide direct evidence about pantoprazole's effect on patients requiring non-invasive ventilation or no ventilatory support. Given contemporary critical care practice, we anticipate that a small proportion of enrolled patients will receive no enteral nutrition, such that inferences about this population will be limited."

** In addition, we have underscored the specific characteristic of our cohort – focusing on patients needing invasive mechanical ventilation - to make this more clear, so the second paragraph of the Status section now reads:

"REVISE re-addresses the benefits, harms, or disutility of acid suppression in invasively mechanically ventilated patients the ICU, aligned with the *Declaration of Helsinki* stating that 'even the best-proven interventions' must be continually re-evaluated through research for their safety, effectiveness, efficiency, accessibility and quality [52]."

4- Limited information about the funding has first come under the legends for Table 2; it should be written in the manuscript and should add some details about hybrid serial funding.

** We are pleased to add detail about funding in the manuscript, and will retain the phrase serial hybrid funding in the legend of Table 2 as well. The new section is called Peer Review Funding, which reads as follows, similar to the funding statement:

"Peer-Review Funding

Global enrolment in REVISE is supported by serial hybrid peer-review funding including 3 grants from the Canadian Institutes of Health Research, one of which is the Accelerating Clinical Trials Fund, and the Hamilton Academy of Health Sciences Organization. The National Health and Medical Research Council of Australia grant funds enrolment in Australia. REVISE was approved by the National Institute for Health Research in the UK as a Portfolio Study, supported by the NIHR Clinical Research Network. The funders have no role in the conception, design, conduct, oversight, analysis, interpretation, write-up, or approval of the manuscript, or decision to submit for publication."

** Also, we have updated the Funding Statement at the end of the manuscript to indicate another Canadian Institutes for Health Research grant from the Accelerated Clinical Trials Funds, awarded in May 2023. The updated Funding Statement reads:

"Funding Statement: Funding Statement: REVISE is funded by peer-reviewed grants [Canadian Institutes of Health Research 201610PJT-378226-PJT-CEBA-18373, Canadian Institutes of Health Research 202207CL3-492565-CTP-CEBA-19215], and the Canadian Institutes for Health Research Accelerating Clinical Trials Fund [ACT Consortium RFA-1 Application], as well as the Hamilton Academy of Health Sciences Organization [HAH-22-009], and funds from St. Joseph's Healthcare Hamilton and McMaster University. The National Health and Medical Research Council of Australia grant [GNT1124675] funds enrolment in Australia. REVISE was approved by the National Institute for Health Research (NIHR) in the UK as a Portfolio Study [CPMS ID 45782], eligible for support from the NIHR Clinical Research Network. [https://www.nihr.ac.uk/researchers/collaborations-services-and-support-for-your-research/run-your-study/crn-portfolio.htm]. This trial received no support from the commercial or private sector. The funders/sponsors have no role in the conception, design, conduct, oversight, analysis, interpretation, write-up, review or approval of the manuscript, or decision to submit the manuscript for publication."

** Thank you for taking the time to offer peer review and much appreciated suggestions for our protocol report. We would like to include you in the Acknowledgement section of this article.

Other improvements:

1) We modified the Abstract Methods and Analysis section to indicate that patients are now enrolled in Brazil. The revision is as follows:

"REVISE is an international, randomized, concealed, stratified, blinded parallel-group individual patient trial being conducted in ICUs in Canada, Australia, Saudi Arabia, UK, US, Kuwait, Pakistan and Brazil."

2) We have indicated that REVISE is enrolling patients in 8 countries, as 3 centers in Brazil have recently joined. This is reflected in an update to the fifth bullet under Article Summary, as follows:

"Enrolment of heterogenous patients in 8 countries will enhance the generalizability of the findings"

Several additions to this protocol manuscript were made in response to the Editor and Reviewer suggestions. We trimmed a few words to try to keep the word count close to 4,000, but the BMJ Open guidance is to let you know if the document is slightly longer. Thank you very much for the chance to improve this protocol report, and for considering our work in BMJ Open.

VERSION 2 – REVIEW

REVIEWER	Skurzak, Stefano Ospedale San Giovanni Battista, Dipartimento di Anestesia e di Medicina degli Stati Critici
REVIEW RETURNED	20-Oct-2023

GENERAL COMMENTS	I would like to thank you for the kind consideration you offered to the remarks raised.

REVIEWER	Kazmi, Syed Sajid Hussain Oslo University Hospital, Department of Vascular Surgery
REVIEW RETURNED	15-Oct-2023

GENERAL COMMENTS	It should be Syed Kazmi in the acknowledgment. REVISE is a randomized, stratified, concealed, blinded, parallel-group Trial. It has a superiority design. Since 2019, the Trial has been conducted in Canada, Australia, Saudi Arabia, the UK, the US, Kuwait, Pakistan and Brazil. According to the authors, PPIs' impact on ICU patients is unclear. They support their statement with the findings of several previously conducted randomized trials where the proportion of clinically significant bleeding was much smaller than that of pneumonia and C. Difficile—besides, their own systematic review and network meta-analysis of the RCTs in 2020 highlighted uncertainties regarding the net effect of PPIs across outcomes of mortality, pneumonia, C. Difficile infections and even in GI bleedings in low-risk groups. The authors claim that the existing trials have failed to exclude substantial harm from PPIs. Their review and meta-analysis from 2020 showed an absolute increase in mortality of 4.2% of the ICU patients. In this revised trial protocol, the authors have provided well-defined aims of the Trial. The patient population is >18 years old, who are expected to remain on a ventilator beyond a calendar day after enrollment and are randomized to either 40 mg pantoprazole IV or an identical placebo daily while on mechanical ventilation in the ICU. This Trial is powered appropriately, following the primary efficacy outcome of clinically important upper GI bleeding within 90 days of randomization. Besides, the sample power is also calculated for 90-day all-cause mortality, considered a primary safety outcome of the REVISE trial. The authors have provided a detailed and relevant account of the revised version's ethical, logistical, and trail funding information. The authors have also provided a summary of the strengths and limitations of this Trial. They seem to have an excellent plan to reduce the risk of bias to ensure the generalization of the results of this Trial. The trial protocol's revised version has no major flaws and can be accepted for publication in BMJ Open.