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)	Nutrition and Exercise in Critical Illness Trial (NEXIS Trial): A protocol of a multi-centered, randomized controlled trial of combined cycle ergometry and amino acid supplementation commenced early during critical illness
AUTHORS	Heyland, Daren; Day, Andrew; Clarke, G. John; Hough, Catherine (Terri); Files, D. Clark; Mourtzakis, Marina; Deutz, Nicolaas; Needham, Dale; Stapleton, Renee

VERSION 1 - REVIEW

REVIEWER	Brenda O'Neill Ulster University, UK
REVIEW RETURNED	28-Jan-2019

GENERAL COMMENTS	Please see below for a few points for clarification, and a few suggestions where further detail could be useful. • Background/rationale - It would be helpful to include further rationale for the specific selection of cycling as the type of exercise • Under randomisation - Patients are excluded if prior hospital stay was > 5 days; should this be included in the Table of EC? • Interventions The study interventions are described but usual care is not except in the abstract where it indicates “usual care (which commonly consists of minimal exercise…..” Is this delivery of “minimal exercise” also the case after ICU d/c (i.e. on the wards during the remainder of the 21 days)? Is this usual care consistent across all the included sites? Table 3 indicates that mobility /rehabilitation received will be recorded at enrolment and during ICU stay – should it be noted that this will also be recorded after ICU discharge until 21days to capture this period also (if this is the case). Is there potential for rehabilitation by different MDT members that might need to be noted/considered e.g. between sites? • Description of cycling - Cycling is expected until ICU d/c or 21 calander days during hospitalisation; is the cycling delivered during one single session only per day? • Primary OM - 6MWT per ATS 2014 “with adaptations as needed.” not sure about the type of adaptation. • Perhaps consider adding some words about what steps will be taken to ensure the cycling intervention will be delivered as intended.

REVIEWER	Marc Nickels Princess Alexandra Hospital, Metro South, Brisbane, Australia.
REVIEW RETURNED	29-Jan-2019

GENERAL COMMENTS	The investigators describe a multi-center Phase 11b RCT that aims to compare outcomes of patients receiving IV amino acid supplementation and cycle ergometry exercise to usual care (typically receive less than target protein and modest participation in exercise interventions). The primary outcome is 6 minute walk test distance. The protocol is well written. The investigators have demonstrated an excellent understanding of current evidence-base. The investigators have analysed the literature to identify a key gap in current rehabilitation studies for patients with acute respiratory failure. The investigators have designed a well thought out study to investigate this key gap of assessing outcomes when nutrition and exercise interventions are combined. The inclusion and exclusion criteria are clear. The addition of rationale for exclusion criteria is a welcome addition to standard exclusion criteria tables. Given this study is already enrolling, I will focus on areas for clarification to enable replication of the intervention and better research reporting. SPIRIT Guidelines and Study Protocol: Inclusion of SPIRIT Guidelines Checklist and the study protocol as supplementary files would assist improve the quality of the submission and subsequent publication to enable replication of the study/ clinical implimention of the inventions if indicated. Exclusion criteria: criteria 9): is there any evidence to that conducting cycle ergometry exercise sessions with a patient on a neuromuscular blocker (NMB) infusion is unsafe? Patients potentially could be cycled passively whilst cardiovascular and cardiorespiratory safety parameters could be observed. To my knowledge the benefit (or lack of benefit) of conducting cycle ergometry sessions with patients on NMB infusions is unknown. By excluding patients on NMB infusions early in their admission may limit the number of patients that could be recruited to this study. This exclusion criteria will also limit generalizability of results to patients who have received NMB infusions over the first 5 days of ICU admission. As patients who receive NBM infusions are at high risk of developing ICU Acquired Weakness this is a key patient group that may benefit from being included in the investigation. Recommendation: Depending on the patient recruitment progress it may be worthwhile amending the study protocol to include patients who are currently receiving NMB infusions. Regarding exclusion criteria 12): patients who have been in hospital for more than 5 days have been excluded from the study due to likelihood of established muscle weakness. Have the investigators considered whether patients admitted to ICU following a recent hospital admission and subsequent discharge (recent hospital re-admission) should be excluded for the same rationale? Consent: What is the participant study consenting process?

	Randomisation: What web-based system is being utilised? Is an investigator responsible for generating a variable size random number sequence and then uploading that sequence into the web-based randomisation system? Cycle ergometry exercise: To enable replication of the cycle ergometry exercise intervention could you please specify: 1. What passive cadence will be used? 2. When a patient is actively cycling what intensity of exercise will be targeted (rate of perceived exertion, cadence etc.)? 3. When and how much resistance be added to the cycling sessions? 4. Will sessions be conducted on weekends? Analysis: How many sessions of cycle ergomety exercise are required to meet intention-to-treat (ITT) principles. Is a per-protocol analysis planned for patients who are randomised to the intervention group but do not complete the number of cycle ergometry exercise sessions to meet ITT principles? Adverse events: This there a safety monitoring committee? If so, does the safety monitoring committee include a representative that is not directly involved in the research? Discussion: As this is a Phase II RCT could the authors please describe the criteria for progressing to a Phase III RCT? Tables and Figures: Recommendations: Inclusion of a tables that outlines safety criteria for commencement and cessation of the cycle ergometry exercise and timelines for outcome measurement. Include a CONSORT diagram to outline planned study design. These tables and figures have consistently been included in cycle ergometry exercise protocols previously published by BMJ Open: • Kho et al. (2016) CYCLE pilot: a protocol for a pilot randomised study of early cycle ergometry versus routine physiotherapy in mechanically ventilated patients. • Nickels et al. (2017) Critical Care Cycling Study (CYCLIST) trial protocol: a randomised controlled trial of usual care plus additional in-bed cycling sessions versus usual care in the critically ill. • Parry et al. (2012) Early rehabilitation in critical care (eRiCC): functional electrical stimulation with cycling protocol for a randomised controlled trial Minor corrections: Page 6 line 49: Capitalise ‘Health’ Page 27 line 30: delete full stop in-between an and unrestricted Page 27 line 52: Capitalise ‘Day’ Clarification: The BMJ Open title page with the submission listed John Clarke as Gregory Clarke in the Complete list of Authors. This appears to be a typo, or mistake during the submission process. Please correct as appropriate. Competing Interests Statement: Author MM is currently not listed in this statement. Please update as appropriate. I commend the investigators for planning and commencing this innovation and needed research. Additionally, I would like to acknowledge the value to the scientific community that will be gained by investigators publishing this protocol. I wish the investigators well, I am looking forward to finding out if combining amino-acid supplementation with cycle ergometry

	exercise has a synergist effect that leads to improved functional outcomes for critically ill patients.

REVIEWER	Dominik Roth, MD, PhD Department of Emergency Medicine Medical University of Vienna, Austria
REVIEW RETURNED	23-Feb-2019

GENERAL COMMENTS	This is a study protocol for a RCT on a combined Intervention (nutrition & exercise) vs. standard care in ventilated patients at the ICU. I did not review the medical rationale of the interventions (i.e. Introduction and Study Intervention sections), but focused on the methods only. General study design and randomization are presented in a concise matter. Regarding randomization, the authors plan stratification both by study site and by length of hospitalisation prior to ICU (<48hrs vs >=48hrs). While this is legitimate, the authors do not report how many patients they expect/plan to include in the two groups. This Information should be added. Blinding as planned seems appropriate for the Intervention. Data collection and selection of outcomes seems appropriate. I have no knowledge whether the primary outcome (6MWT) is a standard test used in the field, and leave this to the experts. In the Outcomes section there is no information on when 6MWT is performed. In the Statistical Analysis section, it is stated, that it is performed at hospital discharge. This should be moved to the Outcomes section. Furthermore, hospital discharge is generally regarded as a weak time-point definition, as it may be dependent on many factors, both medical and non-medical. This might influence the outcome. The authors should therefore comment on their thoughts why this time-point was chosen (vs. a fixed time-point, e.g. 7 days after end of the Intervention), and how they want to deal with possible influence of length of stay on the outcome. At the very least, length of stay both at the ICU and at the hospital shall be reported for both groups. Power calculation seems legitimate (assuming that the expected effect of 50m difference in the 6MWT is clinically feasible), and is done correctly. This includes considerations on deceased patients and those unable to perform the test. SUMMARY OF COMMENTS: Sound statistical methodology. Please add information on patient-distribution between <48h and >=48hrs groups. Please elaborate on timepoint of measurement of the primary outcome.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Brenda O'Neill

Institution and Country: Ulster University, UK

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Please see below for a few points for clarification, and a few suggestions where further detail could be useful.

• Background/rationale - It would be helpful to include further rationale for the specific selection of cycling as the type of exercise

Response: Thank you for your feedback. We have added further explanation to the manuscript to include our Background/rationale.

We chose to utilize in-bed cycling because loss of lean body mass with bed rest is most pronounced in the legs.75,76

Our research finding also demonstrates greater weakness in legs

vs. arms in ICU patients.77 Moreover, leg strength is critical to ambulation, and thus key to functional independence and living at home. 78-83

Under randomisation - Patients are excluded if prior hospital stay was > 5 days; should this be included in the Table of EC?

Response: Thank you for your comment. Our intention is that this is covered under exclusion 12 in the table of exclusions. We have added additional language to help clarify this in the randomisation paragraph. "As such, we have excluded patients if they have spent greater than 5 days admitted to hospital in the 14 days leading up to the current ICU admission."

• Interventions

The study interventions are described but usual care is not except in the abstract where it indicates "usual care (which commonly consists of minimal exercise….." Is this delivery of "minimal exercise" also the case after ICU d/c (i.e. on the wards during the remainder of the 21 days)?

Response:

Our reference to "minimal exercise" refers to the amount of PT/OT that patients typically receive while in ICU as part of usual clinical care. We are considering PT and OT received as part of clinical

care to be included in the standard co-interventions for all patients we described and will report on in the final manuscript. We are measuring the frequency, duration and types of interventions administered for all PT and OT sessions during ICU stay and expect to be the same between groups. We don't collect this information while the study patients are on the hospital wards. We have added PT/OT to the list of co-interventions in the manuscript

"(2) Frequency, duration and intervention type of all physical therapy and occupational therapy sessions in the ICU;"

Is this usual care consistent across all the included sites?

Response: Thank you for your comment. Across our 4 sites, 3 of our sites have very similar standards of usual care. One of the 6 participating ICUs, at one of our sites (Johns Hopkins) delivers a greater amount of baseline exercise to its participants. However, we stratify by site as part of our randomization strategy. This will minimize the impact of differences across sites in our trial.

.Table 3 indicates that mobility /rehabilitation received will be recorded at enrolment and during ICU stay – should it be noted that this will also be recorded after ICU discharge until 21days to capture this period also (if this is the case). Is there potential for rehabilitation by different MDT members that might need to be noted/considered e.g. between sites?

Response: Thank you for your comment. We are not recording any data about the mobility/rehabilitation received after ICU discharge. We are collecting data for all days in the ICU until day 21 including re-admissions. We do acknowledge that there may be differences between sites. Again, this is why we are stratifying by site as part of our randomization strategy.

• Description of cycling - Cycling is expected until ICU d/c or 21 calander days during hospitalisation; is the cycling delivered during one single session only per day?

Response: Thank you for your question. Cycling is ideally delivered in a single session each day. We do have a provision that there is an interruption in a sessions, a second session should be attempted in order to achieve the desired cycling time. The protocol is a 45 minute version adapted from a protocol that has already been published by one of the co senior authors.

Kimawi I, Lamberjack B, Nelliot A, et al. Safety and feasibility of a protocolized approach to in-bed cycling exercise in the intensive care unit: quality improvement project. Phys Ther. 2017;97:593–602.

• Primary OM - 6MWT per ATS 2014 "with adaptations as needed." not sure about the type of

adaptation.

Response: Thank you for your question. The primary adaptation is performing the test only once, rather than twice (that is recommended due to learning effect). This is done due to feasibility reasons, as commonly done when this test is used in critical care studies. We have added the following language to the manuscript to address this:

"The test will only be performed once, rather than twice as recommended due to the feasibility of asking critically ill patients to perform the test multiple times."

• Perhaps consider adding some words about what steps will be taken to ensure the cycling intervention will be delivered as intended.

Response: Thank you for your feedback. We have included the following additional language

"Proper implementation of the cycling will be overseen locally by site investigators and research staff. The data coordinating center will run periodic data reports to review the implementation of the combined intervention. The protocol that is used in this randomized controlled trial is adapted from an existing protocol that was developed and extensively used at one of the study sites."

Kimawi I, Lamberjack B, Nelliot A, et al. Safety and feasibility of a protocolized approach to in-bed cycling exercise in the intensive care unit: quality improvement project. Phys Ther. 2017;97:593–602.

Reviewer: 2

Reviewer Name: Marc Nickels

Institution and Country: Princess Alexandra Hospital, Metro South, Brisbane, Australia.

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

The investigators describe a multi-center Phase 11b RCT that aims to compare outcomes of patients receiving IV amino acid supplementation and cycle ergometry exercise to usual care (typically receive less than target protein and modest participation in exercise interventions). The primary outcome is 6 minute walk test distance.

The protocol is well written. The investigators have demonstrated an excellent understanding of current evidence-base. The investigators have analysed the literature to identify a key gap in current

rehabilitation studies for patients with acute respiratory failure. The investigators have designed a well thought out study to investigate this key gap of assessing outcomes when nutrition and exercise interventions are combined.

The inclusion and exclusion criteria are clear. The addition of rationale for exclusion criteria is a welcome addition to standard exclusion criteria tables.

Given this study is already enrolling, I will focus on areas for clarification to enable replication of the intervention and better research reporting.

SPIRIT Guidelines and Study Protocol: Inclusion of SPIRIT Guidelines Checklist and the study protocol as supplementary files would assist improve the quality of the submission and subsequent publication to enable replication of the study/ clinical implimention of the inventions if indicated.

Response: Thank you for your suggestion. We have completed and attached the SPIRIT guideline checklist. We included additional language and a reference that describes the cycling protocol that we have adapted to a 45 minutes version for our RCT. “The protocol that is used in this RTC is adapted from an existing protocol that was developed and extensively used at one of the study sites”. This will enable others to replicate our study intervention.

Kimawi I, Lamberjack B, Nelliot A, et al. Safety and feasibility of a protocolized approach to in-bed cycling exercise in the intensive care unit: quality improvement project. Phys Ther. 2017;97:593–602.

Exclusion criteria: criteria 9): is there any evidence to that conducting cycle ergometry exercise sessions with a patient on a neuromuscular blocker (NMB) infusion is unsafe? Patients potentially could be cycled passively whilst cardiovascular and cardiorespiratory safety parameters could be observed. To my knowledge the benefit (or lack of benefit) of conducting cycle ergometry sessions with patients on NMB infusions is unknown. By excluding patients on NMB infusions early in their admission may limit the number of patients that could be recruited to this study. This exclusion criteria will also limit generalizability of results to patients who have received NMB infusions over the first 5 days of ICU admission. As patients who receive NBM infusions are at high risk of developing ICU Acquired Weakness this is a key patient group that may benefit from being included in the investigation. Recommendation: Depending on the patient recruitment progress it may be worthwhile amending the study protocol to include patients who are currently receiving NMB infusions.

Response: Thank you for your feedback and suggestion. Standard rehab practice in North America

and elsewhere typically does not conduct rehab during NMB infusion. This temporary type of exclusion criteria is also found in other cycling protocols conducted in North America such as:

Kho ME, Molloy AJ, Clarke FJ, et al. Multicentre pilot randomised clinical trial of early in-bed cycle ergometry with ventilatedpatients. BMJ Open Resp Res2019;6:e000383. doi:10.1136/bmjresp-2018-000383

Kho ME, Molloy AJ, Clarke FJ, Ajami D, McCaughan M, Obrovac K, et al. (2016) TryCYCLE: A Prospective Study of the Safety and Feasibility of Early In-Bed Cycling in Mechanically Ventilated Patients. PLoS ONE 11(12): e0167561. doi:10.1371/journal.pone.0167561

Regarding exclusion criteria 12): patients who have been in hospital for more than 5 days have been excluded from the study due to likelihood of established muscle weakness. Have the investigators considered whether patients admitted to ICU following a recent hospital admission and subsequent discharge (recent hospital re-admission) should be excluded for the same rationale?

Response: Thank you for your Comment. Yes we have considered this and have applied this exclusion criterion in a way that addresses these patients. We have operationalized this exclusion as any patient who have been in hospital for greater than 5 days in the 2 weeks prior to ICU admission. We have clarified this in the randomization section of the manuscript.

Consent: What is the participant study consenting process?

Response: Thank you for your Question. I have included the following addition to the manuscript.

“Once patients have been screened and confirmed by the site investigator or a sub investigator, the participant or legally authorized representative is approached for informed consent. The research staff engages the LAR in a conversation to discuss the trial and ensure they have understood the material. They are given ample time to review the materials and ask any relevant questions.”

Randomisation: What web-based system is being utilised? Is an investigator responsible for generating a variable size random number sequence and then uploading that sequence into the web-based randomisation system?

Response: Thank you for your question. We use a proprietary w

into our web-based system. We have re-written the description of the randomization process to include all required SPIRIT elements and will address your two questions.

“Randomization will be stratified by site and hospital length of stay prior to randomization (<48 hours vs. >48 hours). Randomization will further be restricted by using permuted blocks of

random size within strata. The randomization list was commuter generated by the senior biostatistician at the data coordinating center who is uninvolved with site enrollment and unaware of which site codes map to which sites. The randomization is implemented using the data coordinating center's secure central web-based randomization system which maintains concealment of future allocations and has been used successfully for several large international RCTs."

Cycle ergometry exercise: To enable replication of the cycle ergometry exercise intervention could you please specify:

1. What passive cadence will be used?

Response: Thank you for your question. There are 2 cadences that will be used passively, 10 and 25 rpm. We will alternate between these cadences from one interval to the next. Please refer to the publication provided above.

2. When a patient is actively cycling what intensity of exercise will be targeted (rate of perceived exertion, cadence etc.)?

Response: Thank you for your question. When patients are actively cycling, we will be providing strong verbal encouragement to increase their cadence to the highest level they can achieve. This will be coupled with a graduated approach of increasing resistance when the patients are able to complete 5 minutes or more active cycling in each 10 minute interval. There is no target in terms of perceived exertion scale for this intervention.

3. When and how much resistance be added to the cycling sessions?

Response: Thank you for your question. When patients are actively cycling, we will be using a graduated approach of increasing resistance when the patients are able to complete 5 minutes or more active cycling in each 10 minute interval within a session. On subsequent sessions, patients will start at the 1 gear lower than highest gear they were able to actively cycle for 5 minutes or greater in any of the active intervals on the prior day. Please refer to the publication provided above.

4. Will sessions be conducted on weekends?

Response: Thank you for your question. Yes, cycling will be conducted on weekends during the first 5 study days (given our focus on early intervention) and whenever possible beyond that (i.e. at least 5 of 7 days per week, after the first 5 days of study) for the duration of the ICU stay or until day 21.

Analysis: How many sessions of cycle ergometry exercise are required to meet intention-to-treat

(ITT) principles.

Response: Thank you for your question. All randomized patients will be included in the intention-totreat

analysis regardless of how many cycling sessions they will receive.

Is a per-protocol analysis planned for patients who are randomised to the intervention group but do not complete the number of cycle ergometry exercise sessions to meet ITT principles?

Response: Thank you for your question. Yes, we are planning a per-protocol analysis for those who receive 3 or more days of the combined intervention. We have added corresponding text to the manuscript.

“A per-protocol analysis will also be performed by excluding patients randomized to the intervention arm who do not receive at least 3 days of the combined intervention and patients in the usual care group who stay less than 3 days in the ICU.”

Adverse events: This there a safety monitoring committee? If so, does the safety monitoring committee include a representative that is not directly involved in the research?

Response: Thank you for your question. We have an independent DSMB made up of 5 members. As per our funding body (NIH) standards, all members are not directly involved in the research.

Discussion: As this is a Phase II RCT could the authors please describe the criteria for progressing to a Phase III RCT?

Response: We do not have fixed criteria for progressing to Phase III RCT especially since perspective of funding body would impact this as well. In general, if we observe clinically important result (s), in addition to safety and feasibility, the leadership group of the RCT would carefully consider a Phase III RCT.

Tables and Figures: Recommendations: Inclusion of a tables that outlines safety criteria for commencement and cessation of the cycle ergometry exercise and timelines for outcome measurement.

Response: Thank you for your comment. We have added the safety criteria for commencement and cessation of cycling to the manuscript (See Box 1). The timeline for our outcomes assessments is outlined in figure 1. I have added table 4 which includes a more detailed description of the timeline for the outcomes.

Include a CONSORT diagram to outline planned study design.

These tables and figures have consistently been included in cycle ergometry exercise protocols previously published by BMJ Open:

• Kho et al. (2016) CYCLE pilot: a protocol for a pilot randomised study of early cycle ergometry versus routine physiotherapy in mechanically ventilated patients.

• Nickels et al. (2017) Critical Care Cycling Study (CYCLIST) trial protocol: a randomised controlled trial of usual care plus additional in-bed cycling sessions versus usual care in the critically ill.

• Parry et al. (2012) Early rehabilitation in critical care (eRiCC): functional electrical stimulation with cycling protocol for a randomised controlled trial

Response: Thank you for your comment. The planned study design is outlined in Figure 1. I have also created a consort diagram and added it to the manuscript as Figure 2.

Minor corrections:

Page 6 line 49: Capitalise ‘Health’

Response: This has been corrected

Page 27 line 30: delete full stop in-between an and unrestricted

Response: Thank you, this has been corrected

Page 27 line 52: Capitalise ‘Day’

Response: Thank you, this has been corrected

Clarification: The BMJ Open title page with the submission listed John Clarke as Gregory Clarke in the Complete list of Authors. This appears to be a typo, or mistake during the submission process. Please correct as appropriate.

Response: Thank you for noticing this, I will correct this.

Competing Interests Statement: Author MM is currently not listed in this statement. Please update as appropriate.

Response: Thank you, this has been added.

I commend the investigators for planning and commencing this innovation and needed research. Additionally, I would like to acknowledge the value to the scientific community that will be gained by investigators publishing this protocol.

I wish the investigators well, I am looking forward to finding out if combining amino-acid supplementation with cycle ergometry exercise has a synergist effect that leads to improved functional outcomes for critically ill patients.

Reviewer: 3

Reviewer Name: Dominik Roth, MD, PhD

Institution and Country: Department of Emergency Medicine - Medical University of Vienna, Austria

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

This is a study protocol for a RCT on a combined Intervention (nutrition & exercise) vs. standard care in ventilated patients at the ICU.

I did not review the medical rationale of the interventions (i.e. Introduction and Study Intervention sections), but focused on the methods only.

General study design and randomization are presented in a concise matter.

Regarding randomization, the authors plan stratification both by study site and by length of hospitalisation prior to ICU (<48hrs vs >=48hrs). While this is legitimate, the authors do not report how many patients they expect/plan to include in the two groups. This Information should be added.

Response: Thank you for your comment. At the outset of the trial, we expected equal enrollment across the 4 sites but did not have any reasonable information that allows us to predict how many participants would be in the <48hrs group.

Blinding as planned seems appropriate for the Intervention.

Data collection and selection of outcomes seems appropriate. I have no knowledge whether the primary outcome (6MWT) is a standard test used in the field, and leave this to the experts. In the Outcomes section there is no information on when 6MWT is performed. In the Statistical Analysis section, it is stated, that it is performed at hospital discharge. This should be moved to the Outcomes section.

Response: Thank you for your feedback. We have added a table that outlines the timeline of all assessments.

Furthermore, hospital discharge is generally regarded as a weak time-point definition, as it may be dependent on many factors, both medical and non-medical. This might influence the outcome. The authors should therefore comment on their thoughts why this time-point was chosen (vs. a fixed time-point, e.g. 7 days after end of the Intervention), and how they want to deal with possible influence of length of stay on the outcome. At the very least, length of stay both at the ICU and at the

hospital shall be reported for both groups.

Response: Thank you for your feedback. Length of stay in both ICU and hospital will be reported. We had a great deal of deliberation about using a fixed time point vs. a time point just prior to hospital discharge. We were uncertain of when that fixed time point might be and if we choose an early time point, some patients would be unable to perform the physical assessments. If we chose a later time point, some patients may be discharged from hospital already and it is extremely difficult to obtain these measures once patients are discharged from hospital, thus, we would be left with a great deal of missing data. While we recognize that hospital discharge may be dependent on many factors, it also signifies a benchmark in the recovery process and there is a minimum standard of health that must be achieved by the patients.

This model of using ICU and hospital discharge has been used by several other cycling protocols as well:

Kho ME, Molloy AJ, Clarke FJ, et al. Multicentre pilot randomised clinical trial of early in-bed cycle ergometry with ventilatedpatients. BMJ Open Resp Res2019;6:e000383. doi:10.1136/bmjresp-2018-000383

Kho ME, Molloy AJ, Clarke FJ, Ajami D, McCaughan M, Obrovac K, et al. (2016) TryCYCLE: A Prospective Study of the Safety and Feasibility of Early In-Bed Cycling in Mechanically Ventilated Patients. PLoS ONE 11(12): e0167561. doi:10.1371/journal.pone.0167561

Eggmann S, Verra ML, Luder G, Takala J, Jakob SM (2018) Effects of early, combined endurance and resistance training in mechanically ventilated, critically ill patients: A randomised controlled trial. PLoS ONE 13(11): e0207428. https://doi.org/10.1371/journal.pone.0207428

Fossat G, Baudin F, Courtes L, et al. Effect of In-Bed Leg Cycling and Electrical Stimulation of the Quadriceps on Global Muscle Strength in Critically Ill Adults: A Randomized Clinical Trial. JAMA. 2018;320(4):368–378. doi:10.1001/jama.2018.9592

Power calculation seems legitimate (assuming that the expected effect of 50m difference in the 6MWT is clinically feasible), and is done correctly. This includes considerations on deceased patients and those unable to perform the test.

SUMMARY OF COMMENTS:

Sound statistical methodology.

Please add information on patient-distribution between <48h and >=48hrs groups.

Please elaborate on timepoint of measurement of the primary outcome.

VERSION 2 – REVIEW

REVIEWER	Brenda O'Neill Ulster University, UK
REVIEW RETURNED	08-May-2019

GENERAL COMMENTS	The research team have fully addressed all comments and suggestions. This manuscript is very comprehensive and thoroughly outlines the study protocol.

REVIEWER	Marc Nickels Princess Alexandra Hospital Queensland Health Brisbane, Australia.
REVIEW RETURNED	08-May-2019

GENERAL COMMENTS	The investigators describe a multi-centre Phase 11b RCT that aims to compare outcomes of patients receiving IV amino acid supplementation and cycle ergometry exercise to usual care (typically receive less than target protein and modest participation in exercise interventions). The primary outcome is 6-minute walk test distance. This review is in response to the revised protocol. Thank-you for including the SPIRIT Guideline and further information and reference to enable the cycling intervention to be replicated. Thank you for providing references showing precedent of temporary exclusion due to the infusion of NMB. It appears the safety of early rehabilitation during NMB is yet to be assessed. Thanks for clarifying this exclusion criteria in the randomization section regarding the exclusion of patients admitted for more than 5 days prior to ICU admission within the previous 2 weeks. Thanks for updating the randomization section to include details regarding the web-based system that is being utilised, clarification regarding who is responsible for the random number sequence generation. I believe the updated information covers the recommended components defined in the SPIRT checklist. Thank you for the clarification regarding exercise intensity, resistance, frequency during both passive and active cycling. Thanks for clarifying that the criteria for performing a per protocol analysis. Thank you for clarification regarding the independent DSMB. Thank-you for your response regarding the criteria for progression to a Phase III study. I recommend that a similar statement could be added to the manuscript. Tables and figures: Thank-you for including Box 1 regarding safety criteria for commencing and terminating in-bed cycling sessions, the CONSORT diagram in Figure 2 and more detail regarding outcome assessment timing in Table 4. Overall, the investigators have addressed all of the

	recommendations that I had suggested in their author's response and the majority of the recommendations have been incorporated into the revised protocol. I only have one minor recommendation: please consider incorporating a comment regarding the progression into a future Phase III clinical trial into the manuscript. I wish the investigators all the best with completing this important study.

REVIEWER	Dominik Roth, MD, PhD Department of Emergency Medicine - Medical University of Vienna, Austria
REVIEW RETURNED	02-Jun-2019

GENERAL COMMENTS	The authors addressed all the issues from my previous review. Although they were not able to predict how many patients will be enrolled in the <48hrs and >=48hrs groups, I do not regard this as a major issue.

VERSION 2 – AUTHOR RESPONSE

As the reviewer did not provide any additional questions or concerns, there were no responses required. We did include a statement regarding the criteria for the progression to a Phase III clinical trial at the suggestion of the editor. We also made a small update to the wording of the cycling safety criteria in Box 1. I have also uploaded a copy of our Informed Consent Form at the request of the editor to fulfill item 32 of the SPIRIT guide checklist.