



STUDY PROTOCOL

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# Replacing protein via enteral nutrition in a stepwise approach in critically ill patients: the REPLENISH randomized clinical trial protocol

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## Abstract

**Background** Protein intake is recommended in critically ill patients to mitigate the negative effects of critical illness-induced catabolism and muscle wasting. However, the optimal dose of enteral protein remains unknown. We hypothesize that supplemental enteral protein (1.2 g/kg/day) added to standard enteral nutrition formula to achieve high amount of enteral protein (range 2–2.4 g/kg/day) given from ICU day 5 until ICU discharge or ICU day 90 as compared to no supplemental enteral protein to achieve moderate amount enteral protein (0.8–1.2 g/kg/day) would reduce all-cause 90-day mortality in adult critically ill mechanically ventilated patients.

**Methods** The REPLENISH (Replacing Protein Via Enteral Nutrition in a Stepwise Approach in Critically Ill Patients) trial is an open-label, multicenter randomized clinical trial. Patients will be randomized to the supplemental protein group or the control group. Patients in both groups will receive the primary enteral formula as per the treating team, which includes a maximum protein 1.2 g/kg/day. The supplemental protein group will receive, in addition, supplemental protein at 1.2 g/kg/day starting the fifth ICU day. The control group will receive the primary formula without supplemental protein. The primary outcome is 90-day all-cause mortality. Other outcomes include functional and quality of life assessments at 90 days. The trial will enroll 2502 patients.

**Discussion** The study has been initiated in September 2021. Interim analysis is planned at one third and two thirds of the target sample size. The study is expected to be completed by the end of 2025.

**Trial registration** ClinicalTrials.gov Identifier: [NCT04475666](https://clinicaltrials.gov/ct2/show/study/NCT04475666). Registered on July 17, 2020.

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**Keywords** Critical illness, Protein intake, Randomized controlled trial, Mortality, Functional outcomes

## Background

During the acute phase of critical illness, amino acids are mobilized into the circulation in response to stress hormones to be used in tissue repair and synthesis of acute-phase proteins and other inflammatory mediators [1, 2]. The resulting protein catabolism may lead to immunosuppression [3], poor wound healing [4], and ICU-acquired weakness, which are associated with increased mortality and delayed recovery [5]. Higher protein intake has been thought to mitigate the negative protein catabolic state by increasing the availability of exogenous amino acids. Consequently, clinical practice guidelines have generally recommended the administration of higher protein intake in critically ill patients than in healthy individuals (World Health Organization recommendations: 0.7–0.8 g/kg/day) [6]; however, the supportive data are limited. Observational studies showed inconsistent association between protein intake and outcomes in critically ill patients, with some studies showing that more protein was associated with better outcomes [7–13], others with worse outcomes [14–16], and others with no difference in outcomes [17]. There is scarce evidence from randomized clinical trials (RCTs) that compared higher versus lower protein doses in ICU patients [18–21]. A meta-analysis of 5 RCTs showed no difference in mortality with the use of higher compared to lower protein intake [22]. The inconsistent evidence has been reflected in the variable protein doses recommended in clinical practice guidelines [23, 24].

Additionally, the optimal timing of higher protein intake is unknown. Because protein breakdown is more pronounced in the early phase of illness, it has been suggested that higher protein intake should be given early [13]. On the other hand, there are data suggesting that higher protein intake in the early phase of critical illness may cause harm, which may be related to inhibition of autophagy and increased ureagenesis, leading to greater muscle wasting, and delayed recovery [25–28].

With the current state of evidence, the optimal amount of protein intake in critically ill patients remains largely unclear and is considered a high priority for research [29–32]. The objective of this multicenter RCT is to evaluate whether supplemental enteral protein (1.2 g/kg/day) added to standard enteral nutrition formula to achieve high amount of enteral protein (range 2–2.4 g/kg/day) given from ICU day 5 or until ICU discharge up to ICU day 90 as compared with no supplemental enteral protein to achieve moderate amount enteral protein (0.8–1.2 g/

kg/day) will reduce all-cause 90-day mortality in adult critically ill patients.

## Methods

### Study design and setting

The REPLENISH (Replacing Protein Via Enteral Nutrition in a Stepwise Approach in Critically Ill Patients) trial is an open-label, parallel group, multicenter superiority RCT that is conducted in ICUs in Saudi Arabia and Kuwait. The study has been approved by the Institutional Review Boards of all the participating sites and sponsored by King Abdullah International Medical Research Center, Riyadh Saudi Arabia (RC19/414/R). It has been registered at ClinicalTrials.gov (NCT04475666).

SPIRIT checklist was used when writing this protocol and is attached as a [supplementary file](#).

### Study population

All the patients will be screened for the eligibility criteria (Table 1) on ICU calendar day 4, up to the morning of ICU calendar day 5. The ICU admission calendar day is considered ICU day 1.

#### Inclusion criteria

1. Age  $\geq$  18 years old
2. The patient is started on enteral nutrition via feeding tube (nasoro-gastric, nasoro-enteral, gastrostomy or jejunostomy tubes)
3. The patient is on invasive mechanical ventilation and unlikely to be discharged from the ICU the next day

#### Exclusion criteria

1. Lack of commitment to full life support or brain death. Patients with “Do-Not-Resuscitate” order but with commitment to ongoing life support can be enrolled
2. The patient is on any amount of parenteral nutrition (PN) in ICU at the time of screening, whether PN is used alone or in combination with enteral nutrition. Non-nutritional calories (dextrose, propofol, citrate) not considered as PN
3. The patient has received an average protein of more than 0.8 g/kg/day in the first 4 ICU days
4. The patient is fed entirely through oral route—i.e., those who are eating
5. The patient has hepatic encephalopathy or Child C liver cirrhosis

6. The patient is admitted because of burn
7. The patient has an inherited defect of amino acid metabolism
8. The patient has allergy to protein supplement
9. Pregnancy
10. Prisoners or those undergoing forced treatment

### Consent and recruitment

The research team will approach the patient or surrogate decision maker for consent according to local regulations. Because both feeding strategies are within the standard of care and because enrollment needs to be done early to initiate the feeding strategy, deferred consent can be used if consent could not be obtained a priori. The research coordinator will maintain a screening log of eligible patients who are not randomized.

### Randomization

Enrolled patients will be randomized by the research coordinator through a web-based system at a 1:1 ratio to the supplemental protein group or control group using permuted variable undisclosed block sizes. The allocation sequence is generated by the Database Management Department at King Abdullah International Research Center. Randomization will be stratified by the trial site, the use of renal replacement therapy at the time of randomization, and whether the patient is a suspected or confirmed case of COVID-19.

Co-enrollment in other RCTs is permitted after approval by both trial steering committees.

**Table 1** Eligibility criteria for the study

#### Inclusion criteria

- Age  $\geq$  18 years old
- Patient started on EN via nasogastric/orogastric or duodenal or PEG or jejunostomy tubes
- The patient is on invasive mechanical ventilation and unlikely to be discharged from ICU the next day

#### Exclusion criteria

- Lack of commitment to full life support or brain death
- Patients on any amount of parenteral nutrition (PN) in ICU at the time of screening
- Patients who received an average protein of more than 0.8 g/kg/day in the first 4 ICU days
- Patients fed entirely through oral route—i.e., those who are eating
- Pregnancy
- Burn patients
- Prisoners or those undergoing forced treatment
- Patients with hepatic encephalopathy or Child C liver cirrhosis
- Inherited defect of amino acid metabolism
- Allergies to protein supplement

## Nutrition in the two study groups

### Energy in both groups

Until ICU calendar day 4, the prescription of energy will be left to the discretion of the treating teams. Energy expenditure can be determined using the predictive equations or indirect calorimetry, based on the practice at individual sites. Between days 5 and 90, the energy target is 70 to 100% of calculated or measured energy requirements. Energy intake will be calculated taking into consideration intravenous dextrose, citrate, and propofol. Energy intake will include the administered protein in the primary formula.

### Protein pre-randomization (ICU calendar days 1–4)

Until ICU day 4, protein requirement will be provided according to the local practice as long as no intravenous amino acids are given and the average protein intake in the first 4 days does not exceed 0.8 g/kg/day.

### Protein post-randomization (ICU day 5–ICU discharge) in the control group

The subjects randomized to the control group will receive standard prescription without supplemental proteins (maximum 1.2 g/kg/day) from the primary polymeric formula. No supplemental protein will be allowed. For patients with BMI  $<$  30 kg/m<sup>2</sup>, we will use pre-ICU actual body weight and if unavailable the weight on ICU admission. For patients with BMI  $\geq$  30 kg/m<sup>2</sup>, we will use adjusted body weight (Table 2) [24].

### Protein post-randomization (ICU day 5 to ICU discharge) in the supplemental protein group

The subjects randomized to the supplemental protein group will receive the standard amount of proteins (maximum 1.2 g/kg/day) from the primary formula with the addition of supplemental enteral protein at 1.2 g/kg/day. Supplemental protein is administered using a pure protein formula as boluses by syringe through the feeding tube with flushes with a minimum of 30–60 ml of water. The choice of supplemental protein formula is left to the local teams as per availability. In patients who miss some of the supplemental protein doses because of feeding interruption, the nurse may compensate for the missed dose within the same day. Additionally, in patients with volume overload due to conditions like renal failure or congestive heart failure, we will consider reducing the mixing fluid for the supplemental protein to half (50%) of the calculated amount.

## Co-interventions

- a. PN: Patients on any amount of PN at the time of screening will not be enrolled in the trial. However, patients who have been enrolled in the trial

- and deemed to need PN by their treating team will remain in the trial.
- b. Glucose management: All centers may use their own standard protocols as long as the target blood glucose is between 4.4 and 10 mmol/L (80–180 mg/dl).
  - c. Mobility assessment: All centers may use their own standard protocols with regards to mobility in ICU patients. Data on mobility will be collected.
  - d. Medications: Data on corticosteroids and statins will be collected during the ICU stay (Up to day 90). No concomitant treatments are prohibited in this pragmatic trial.
  - e. Selection of enteral nutritional formula: The type of formula will be left to the discretion of the attending physician. The types of formula used are grouped as general or disease non-specific (for example: Osmolite, Resource, Resource plus, Ensure, Ensure plus, Jevity 1.0, and Jevity 1.2) or disease specific (for example: Pulmocare, Glucerna, Suplena, Peptamen 1.0, Peptamen 1.2, Peptamen 1.5, Novasource Renal, Nepro, Nutren hepatic, Promote, and Vivonex plus).
  - f. The enteral feeding protocol: Each ICU may use their own enteral feeding protocol. The use of prokinetics and type of feeding tube (large-bore nasogastric tube or small-bore nasogastric tube with or without guide wire) is left to the treating team.
  - g. Multivitamins/micronutrients: Most of the used enteral formulae include multivitamins and micronu-

trients. In addition, all patients included in the trial in both arms will receive additional enteral multivitamins/micronutrients as per local formulary.

**Duration of the intervention**

The study intervention will continue until meeting any of the following criteria: death, ICU discharge or day 90 in ICU, premature stopping of feeding due to brain death or palliative care plan whichever comes first, initiation and tolerating of full oral feeding for more than 24 h (i.e., treating physicians feel that enteral nutrition is no longer required). In these situations, the study intervention will no longer be followed, and nutrition will be at the discretion of the treating teams but outcome data will be collected. In addition to this, if patients are withdrawn from the intervention by the family or treating physician, we will continue the data collection and follow-up procedures if the consent to do so is obtained from the surrogate decision maker (SDM). Alternatively, the study procedures will be stopped.

Figure 1 shows the schedule of enrollment, intervention, and assessment for the trial according to the SPIRIT template.

**Data collection**

Baseline data collected from ICU days 1 to 4 will include age, sex, admission category (medical, postoperative (non-trauma) and trauma (post-operative and

**Table 2** Daily protein provision for patients enrolled in the trial

		ICU days 1–4	ICU day 5-ICU discharge or day 90
<b>Standard protein group</b>	Calories	70–100% of calculated (by equations) or measured (by indirect calorimetry) energy expenditure using local standards	70–100% of calculated (by equations) or measured (by indirect calorimetry) energy expenditure using local standards
	Protein	Local standards No intravenous amino acids Protein intake on average not to exceed 0.8 g/kg/day	Local standards (maximum 1.2 g/kg/day, actual body weight for BMI < 30 kg/m <sup>2</sup> and adjusted body weight <sup>a</sup> for BMI ≥ 30 kg/m <sup>2</sup> , from the feeding formula) No supplemental protein
<b>Replenish protein group</b>	Calories	70–100% of calculated (by equations) or measured (by indirect calorimetry) energy expenditure using local standards	70–100% of calculated (by equations) or measured (by indirect calorimetry) energy expenditure using local standards
	Protein	Local standards No intravenous amino acids Protein intake on average not to exceed 0.8 g/kg/day	Local standards (maximum 1.2 g/kg/day, actual body weight for BMI < 30 kg/m <sup>2</sup> and adjusted body weight for BMI ≥ 30 kg/m <sup>2</sup> , from the feeding formula) + Supplemental protein 1.2 g/kg/day actual body weight for BMI < 30 kg/m <sup>2</sup> and adjusted body weight for BMI ≥ 30 kg/m <sup>2</sup> , given as 4–6 boluses per day or infusion

BMI Body mass index

<sup>a</sup> Calculation of adjusted body weight

Step 1: Calculate ideal body weight as follows:

For men: 50 + (0.91 × [height in centimeters – 152.4])

For women: 45.5 + (0.91 × [height in centimeters – 152.4])

Step 2: Calculate adjusted body weight as follows:

Ideal body weight + 0.4 \* (actual weight – ideal body weight)

non-operative)), comorbidities (defined as per the Acute Physiology and Chronic Health Evaluation (APACHE) II system), APACHE II score, simplified mortality score (SMS) [33], Sequential Organ Failure Assessment (SOFA) score on day 4, pre-morbid functional assessment using SARC-F screen for sarcopenia [34] and Nutrition Risk in Critically ill (NUTRIC) score [35]. For patients with COVID-19, additional baseline labs including ferritin, interleukin-6, lactate, and procalcitonin will be collected. Daily data collected from ICU days 1 to 90 or ICU discharge will include nutritional data including energy and protein administered daily, blood glucose and insulin data, vasopressor use, use of renal replacement therapy, use of invasive mechanical ventilation, creatinine, blood urea nitrogen, and urine output. Additional data collected on days 4, 7, 14, 21, and 28 will include mobility level assessment [36], and optional labs for selected sites only (prealbumin, albumin, ammonia, 24-h urine for urinary urea nitrogen, lowest potassium level, lowest magnesium level, lowest phosphate level, aspartate transaminase, alanine aminotransferase and international normalized ratio). In case the labs have multiple readings in a day, the worst values will be recorded.

**Outcome measures**

The primary outcome is 90-day all-cause mortality. Secondary outcomes are days alive at day 90 without life support (use of vasopressor/inotropic support,

invasive mechanical ventilation and/or renal replacement therapy), days alive and out of the hospital at day 90, bacteremia until 2 days post ICU, new or progression of sacral skin pressure ulcers in ICU [37], functional assessment using SARC-F screen for sarcopenia [34], and EuroQoL (EQ)-5D-5L) at day 90. Safety outcomes are classified into major and minor safety outcomes. Major safety outcomes are new episode of stage 2 or higher acute kidney injury by KDIGO criteria [38] after enrollment, newly confirmed pneumonia according to the modified CDC criteria [39], grade IV acute gastrointestinal injury [40], including any of bowel ischemia with necrosis, clinically important gastrointestinal bleeding, Ogilvie’s syndrome, and abdominal compartment syndrome. Additionally, minor safety outcomes will be recorded as one or more of the following: feeding intolerance, diarrhea [40] and refeeding syndrome [41, 42] (Supplementary file 1 Table 2).

**Trial management**

- a. *Steering committee:* The study steering committee will be responsible for overseeing the management of the trial, providing training and support to participating centers for protocol adherence, upholding or modifying study procedures as needed and the statistical analysis plan. This will be achieved through virtual or in-person meetings every 3–6 months.

Study Period																				
	Screening			Enrollment	Post-allocation															Close-out
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D*	D21	D*	D28	D*	D90
<b>Screening and randomization</b>																				
Eligibility criteria	x	x	x	x																
Informed consent	x	x	x	x																
Randomization				x																
Intervention																				
<b>Data collection</b>																				
Baseline	x	x	x	x																
Feeding data																				
Safety data																				
Weekly labs				x			x							x		x		x		
Co-interventions																				
<b>Outcome data</b>																				
Mortality																				x
Length of stay																				x
Functional assessment																				
SARC-F				x																x
EQ-5D-5L																				x

\*Signifies days 15, 16, 17, 18, 19, 20, 22, 23, 24, 25, 26, 27 and 29 to 89; SARC-F: Screening test for sarcopenia; EQ-5D-5L: EuroQoL

**Fig. 1** Timeline for screening, enrollment, and assessment for patients enrolled in REPLENISH trial. Asterisk (\*) symbol signifies days 15, 16, 17, 18, 19, 20, 22, 23, 24, 25, 26, 27, and 29 to 89; SARC-F, screening test for sarcopenia; EQ-5D-5L, EuroQoL 5-Dimension 5-Level questionnaire

- b. *Blinding*: This is an open-label trial. However, the study has two biostatisticians; the one who is blinded to group assignment will be involved in the study design and analysis, and the other who is unblinded will be involved in generating a closed report to the Data Safety Monitoring Board (DSMB) with unblinded group data.
- c. *Ethics approval*: The study has been approved by the Institutional Review Board of the Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia. All participating sites will obtain approval from the related Institutional Review Boards. The study will be conducted in accordance with the ethical principle of the Declaration of Helsinki and International Council for Harmonization–Good Clinical Practice guidelines.
- d. *Data management*: Patient data will be de-identified and stored in a secure server at King Abdullah International Medical Research Center, Riyadh. The database will be password protected, and the participating sites will have a unique credentials to access the database.
- e. *Protocol compliance*: Several measures will be taken to ensure optimal compliance with the study protocols. Before launching the study, ICU physicians, nurses, and dietitians will attend training sessions, with special emphasis on achievement of the protein target as per protocol. Follow-up training sessions will be conducted periodically to provide feedback. Data from each site will be monitored regularly by the project manager and steering committee, and regular reports will be sent to sites regarding the amount of protein delivered in each group and causes of feeding interruptions with suggestions to improve compliance.
- f. *Loss-to-follow-up*: Patients will be followed post ICU discharge (without further intervention) to document hospital vital status. If a randomized patient at any point decides to withdraw from the trial intervention at the request of either the patient himself/herself, family, or the treating physician, the data will be included in the group to which they were allocated as per the intention-to-treat principle and the reason of withdrawal will be documented.
- g. *90-day follow-up*: 90-day outcomes will be documented from the chart or registries or, if needed, by a telephonic interview from the patient or next of kin if the patient is discharged alive. Ninety-day follow-up will include vital status, date of death if the patient is dead, and functional assessment using SARC-F screen and EuroQoL (EQ)-5D-5L if the patient is alive on that day.
- h. *Safety monitoring*: Serious adverse events that are suspected related to research procedures will be

reported as per local guidelines. However, the trial involves a low-risk intervention, and the two levels of protein intake under study (high versus low) are within the recommended ranges of protein supplementation to ICU patients by most clinical practice guidelines. Therefore, it is anticipated that most of adverse events occur as part of the participants' natural disease process. Safety outcomes as well as serious adverse events will be reported to the DSMB. As per local regulations, the hospital in which the study is performed is responsible for treating patients who may suffer any adverse event that is related to the study.

## Statistical methods

- a. *Sample size*: We anticipate a baseline 90-day mortality of 30% and an absolute risk reduction of 5% with the high-protein intervention. The baseline risk was estimated based on a similar cohort from the Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults (PermiT) and Pantoprazole in Patients at Risk for Gastrointestinal Bleeding in the ICU (SUP-ICU) trials. In the PermiT trial which included patients from 7 sites in Saudi Arabia and Canada [43], 715 patients received mechanical ventilation for >4 days, and 209 died by day 90 (29.3%). In the SUP-ICU trial [44], which enrolled acutely admitted ICU patients with at least one risk factor for GI bleeding in 33 ICUs in 5 countries in Northern Europe, 48% (1571/3282) of all included patients were mechanically ventilated on day 4. Of these, 34% (530/1571) died on day 90. The treatment effect in REPLENISH trial (5% absolute risk reduction in 90-day mortality) was based on a propensity-score adjusted analysis which showed an odds ratio for the association of high protein compared to a moderate protein of 0.80 (95% CI 0.56, 1.16,  $p=0.24$ ) [17]. The final analysis of the primary outcome will be based on a two-sided alpha ( $\alpha$ ) of 0.05 and power ( $1-\beta$ ) of 0.80. Based on these assumptions, we need 1251 patients in each group (2502 in both groups).
- b. *Statistical analysis*: The analyses will be done in the intention-to-treat population defined as all randomized patients for whom there is consent for the use of data. Baseline characteristics will be summarized as numbers and percentages (categorical variables), and continuous variables will be summarized as medians and first and third quartiles (Q1, Q3) or means and standard deviation. We will compare the proportions for the primary and secondary outcomes between patients randomized to standard protein

versus high-protein group. We will calculate the relative risk reduction, absolute risk reduction, and the number needed to treat to prevent one death. We will present the primary result with 95% confidence intervals and a 2-sided  $p$ -value (5% level of significance). A detailed statistical analysis plan will be developed and published before trial completion, which includes analysis plan for primary and secondary outcomes and management of missing variables. Each component of the composite outcomes, such as serious adverse events and use of life support, will be reported in a supplement to the primary publication, but any differences between these single components will not be analyzed.

- c. *Subgroup analyses:* The following prespecified subgroups will be analyzed based on admission category: medical vs postoperative vs trauma patients. In addition, we will evaluate the effect of the intervention within subpopulations of our enrolled patients: admission diagnosis of sepsis versus others, vasopressor use at the time of enrollment versus none, acute kidney injury at enrollment (4 KDIGO groups: 0, 1, 2, 3), COVID-19 status versus no COVID-19, BMI of  $\leq 30$  or  $> 30$  kg/m<sup>2</sup>, high nutritional risk (NUTRIC score of 5–9) versus low nutritional risk (NUTRIC score of 0–4) and SARC-F score of  $< 4$  versus  $\geq 4$ .
- d. *Interim analysis:* Interim analysis is planned when 33% and 67% of the sample size has been achieved. The trial may be stopped for safety (based on mortality) ( $p < 0.01$ ) or effectiveness ( $p < 0.001$ ) or if there is other compelling evidence that the trial participants are being harmed. There will be no plans to terminate the trial for futility. We will account for alpha spending by the O'Brien Fleming method and the final significance level will be 0.048 [45].

## Discussion

In this REPLENISH trial, we hypothesize that supplemental enteral protein started on the fifth ICU day in addition to standard enteral nutrition will improve the survival of adult critically ill patients compared to standard enteral nutrition alone. The results of the trial address an important question in enteral nutrition in critically patients.

The study design took in consideration multiple factors as learnt from a pilot study (the REPLENISH pilot trial) [46]. In the current study, we follow a pragmatic approach to eligibility criteria, management of protein and energy intake, and selection of outcome measurements [46]. For example, with the exception of protein intake, all other aspects of nutrition management were left to the treating teams. The administration of protein

as boluses instead of infusion facilitates a closer achievement of protein targets.

## Trial status

The trial started in September 2020 and has recruited 1027 patients from 15 sites in Saudi Arabia and two in Kuwait. The study was started according to the protocol in its third version dated June 03, 2020. There have been minor protocol modifications after starting the trial (versions 4 and 4.1). These changes have no impact on the study conduct. The trial is expected to complete patient follow-up by the end of 2025. Upon completion, the results of the trial will be submitted to a peer-reviewed journal. Authorship will be guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (URM) developed by ICMJE.

## Abbreviations

APACHE	Acute Physiology and Chronic Health Evaluation
DSMB	Data safety monitoring board
ESPEN	European Society for Clinical Nutrition and Metabolism
ICU	Intensive care unit
KDIGO	Kidney Disease: Improving Global Outcomes
PN	Parenteral nutrition
RCT	Randomized controlled trial
SOFA	Sequential Organ Failure Assessment

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13063-023-07507-6>.

**Additional file 1: Table 1.** REPLENISH Trial Management/Steering committee, Data Safety Monitoring Board members and Site collaborators. **Table 2.** Study outcomes and their definitions.

**Additional file 2:** Study proposal.

**Additional file 3:** SPIRIT checklist.

## Acknowledgements

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### Authors' contributions

YA is the chief investigator who contributed to the conception, design, and development of the protocol, analytical plan, and drafting and critical revision of the manuscript for important and intellectual content. HMD, MS, DM, HG, FH, AM, AG, GM, AF, AK, AB, KM, KG, GR, JC, HIA, MHS, NA, RH, KS, MA, RQ, AQ, MH, HA, SQ, AG, SB, AO, SF, MA, OA, AAM, MO, OD, JJ, JS, JCP, AP, and AD contributed to the development of the protocol and critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

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### Availability of data and materials

The data that will support the findings of this study are available from the corresponding author upon reasonable request as per the regulations of King Abdullah International Medical Research Center (KAIMRC).

### Declarations

#### Ethics approval and consent to participate

The study protocol as well as the informed consent have been approved by the National Guard Health Affairs Institutional Review Board (RC19/414/R), Riyadh, and the respective Institutional Review Boards of all the other centers.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

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