Author’s response to reviews

Title: Lung Ultrasound Guided Fluid Management Protocol for the Critically Ill Patient: study protocol for a multi-centre randomized controlled trial

Authors:

Daniel-Mihai Rusu (rusu.daniel.ro@gmail.com)
Ianis Siriopol (ianis.siriopol@gmail.com)
Ioana Grigoras (ioana.grigoras.ro@gmail.com)
Mihaela Blaj (miblaj@yahoo.com)
Adi-Ionut Ciumanghel (adi.ionut80@yahoo.com)
Dimitrie Siriopol (dimitrie.siriopol@yahoo.com)
Ionut Nistor (ionutni@yahoo.com)
Mihai Onofriescu (onomihai@yahoo.com)
Gigel Sandu (gigelsandu@gmail.com)
Beatrice Cobzaru (andrabeatrice@yahoo.com)
Dragos Scripcariu (dscripcariu@gmail.com)
Olguta Diaconu (Olg-d@yahoo.com)
Adrian Covic (accovic@gmail.com)

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Author’s response to reviews:

Dear editors,

We highly appreciate your response regarding our manuscript entitled “Lung Ultrasound Guided Fluid Management Protocol for the Critically Ill Patient: study protocol for a multi-centre randomized controlled trial (Manuscript ID: TRLS-S-18-01067)”.

We are very grateful for the critics and comments provided by the editor and by the manuscript reviewers, which helped us improve our paper. Please see below our point-by-point response to the reviewers’ comments.
All modifications appear in red in the revised version of the manuscript. All authors have approved the revision.

Thank you for your consideration,
Ioana Grigoras, MD, PhD, on behalf of the authors

Authors' response to Reviewers reports

Melanie Meersch (Reviewer 1)

Thank you for the opportunity to review this manuscript reporting the protocol of a multicenter randomized controlled trial, assessing the effectiveness of a lung-ultrasound guided fluid management in critical care with regard to patient outcomes.

I consider your research question highly interesting and very topical. Your study design seems to be appropriate, well-conceived and comprehensive.

Response: Thank you for taking the time to review our manuscript and share your comments on our study protocol.

The authors may consider the following proposals:

1) You considered the dependency of ultrasound data with the investigator in the list of strengths and limitations of the study protocol. To provide a quantification of inter-rater reliability of your investigators, did the authors run a pilot phase with ultrasound examinations of several patients carried out by all investigators to compare the consistency of same-patient-results?

Response: Thank you for your comment. During study preparation all investigators involved in performing LUS were assessed for the ability to perform LUS, to identify B-lines, and to determine BLS. The inter-rater reliability was evaluated by analysing their scores using intraclass correlation coefficient. A quantification of inter-rater reliability will be provided in the final manuscript presenting the trial results.

2) The protocol needs more explanation in the text: What diuretics are used? What exactly means negative fluid balance (-10, -500, -1000)? What if negative fluid balance is not reached through the use of diuretics? What is the maximum dose of diuretics? This might have an influence on the occurrence of AKI consequently affecting patients' outcome. What modality of RRT will be used if negative fluid balance is not achieved?
Response: Thank you for allowing us to explain in detail our trial intervention.

In Methods/Design (Study interventions) we detailed the description of furosemide regimen:

” The ICU physician may recommend fluid therapy or vasoactive drugs with types and amounts at his/her choice. However, when signs of moderate/severe pulmonary congestion are seen on LUS exam (BLS ≥15), a negative 24-hour fluid balance (250-1000 ml) will be intended according to clinical judgement.

To achieve this goal a protocolized intravenous administration of furosemide will be used, under careful monitoring of diuretic response. Diuretic administration will start with a furosemide dose ≤80 mg/day which will be further adapted based on the next 24-hour fluid balance, the follow-up BLS, and the previous diuretic regimen. If a negative fluid balance of more than 1000 ml/24 hours is obtained, and BLS is still ≥15, the initial dose of diuretic will be reduced. If a negative fluid balance of less than 1000 ml/24 hours is obtained and BLS is still ≥15, the administered diuretic dose will be maintained. If negative fluid balance is not achieved and BLS is still ≥15, the dose of diuretic will progressively be increased until the goal is attained. The maximum dose of Furosemide will not exceed 800 mg/day.”

In the same section we explained the modality of RRT to be used if depleting overhydrated patients with diuretics fails:

” For RRT, the treating physician may choose between slow continuous ultrafiltration, continuous veno-venous hemofiltration, continuous veno-venous hemodialysis or continuous veno-venous hemodiafiltration. Along with the goal of rebalancing fluid status, the choice of RRT technique should rely on patients’ particularities and other goals of homeostasis restoration.”

3) As fluid management includes the prevention of hypervolemia as well as the avoidance of a hypovolemic state, both ends of the scale should be displayed equally well. Nevertheless, the intervention of lung ultrasound is an appropriate tool to detect signs of hypervolemia, but does not allow a differentiation of a normal or a hypovolemic condition. According to the protocol, for identification of hypovolemia a fall in blood pressure or an increase in creatinine blood level being felt to be associated with intravascular fluid depletion is intended. These criteria seem to have a rather low level of discrimination, so why not also use ultrasound (measurement of inferior vena cava, 4-chamber view) to detect or exclude hypovolemia?

Response: Thank you for your pertinent comment.

The study aims to investigate the ability of LUS to early identify fluid overload and to guide depletive therapy. Avoidance of hypovolemia is equally important in ICU patients. Evaluation of hypovolemia and its correction will be performed according to usual practice in both arms.
According to routine clinical practice in both ICU’s, criteria to diagnose hypovolemia include the measurement of inferior vena cava collapsibility.

4) Why did the authors decide to use APACHE ≥10 or SOFA≥6 as inclusion criteria?

Response: Thank you for allowing us to explain these inclusion criteria.

We proposed the use of APACHE II and SOFA scores in order to characterize the severity of the condition, mainly in medical ICU patients. The proposed cut-off values allow the inclusion of a large variety of ICU patients, who potentially benefit of the algorithm.

5) How did the authors decide to perform a safety interim analysis after 100 patients? Is only 1 safety interim analysis planned?

Response: One safety interim analysis was planed before the start of the trial for the purpose of analyzing the possible side-effects associated to the use of diuretics or renal replacement therapy.

6) Power calculation: please explain in more detail the expected 10% mortality reduction.

Response: Thank you for your suggestion.

We expect a 10% reduction in mortality based on a large cohort study of ICU patients, which showed a mortality rate difference in fluid overloaded versus non fluid overloaded patients of about 3% WITHOUT ANY INTERVENTION. Using a protocolized depletive therapy we expect to increase this difference.

7) Cardiac assist devices may interfere or hamper the diagnostic utility of LUS. This is not an exclusion criterion, right? If not, please include this as limitation.

Response: Thank you for your suggestion.

In the section Strengths and limitations of the study protocol we added "cardiac assist devices" to the list of the conditions that may interfere with LUS examination:

” Patients with pulmonary conditions known to interfere with BLS evaluation (pneumectomy, pulmonary fibrosis, persistent pleural effusion) will be excluded, but other conditions as obesity, extrapulmonary diseases in the examination area, cardiac assist devices or wound dressing, may also render the LUS examination difficult.”

Minor points
* Please explain the abbreviations at first mentioning starting in the background section.
Response: We explained the abbreviation at first mentioning in the Background section.

* Please revise for spelling errors.
Response: Thank you for your careful reading. We corrected the spelling errors in the revised version of the manuscript.

* Figure 1: please add more details to the table.
Response: Thank you. We revised the Figure 1: The schedule of study procedures (SPIRIT figure) and added more explanation to the table.

Robin McKinney, MD (Reviewer 2)

SUMMARY. - Grigoras et al submitted to TRIALS a manuscript detailing the research protocol of a randomized controlled trial entitled "Lung Ultrasound Guided Fluid Management Protocol for the Critically Ill Patient: study protocol for a multi-centre randomized controlled trial". The problem addressed by this trial is the fluid overload frequently seen in patients admitted to the ICU after fluid resuscitation. They plan to use lung ultrasound to assess volume status and guide fluid resuscitation or fluid removal with diuretics based on the results of the lung ultrasound. Their hypothesis is that lung ultrasound guided fluid management will lead to lower mortality than standard care. This is a clinically significant outcome. Trial status: patient enrollment in the trial started in November 2017 and is expected to end in October 2019.

Response: Thank you for your careful revision of our manuscript.

MAJOR COMPULSARY REVISIONS

ABSTRACT (< 350 words). - The list of keywords must be moved to the end of the manuscript.

Response: We have moved the list of keywords at the end of the manuscript.

METHODs

The objectives paragraph should be stated in the introduction. The objectives of the study should not be stated in the methods section. The procedure that will be performed should be laid out in a step by step fashion.
Response: Thank you. We have moved the objectives paragraph after the Study hypothesis section.

The settings section: The rationale for the sites chosen does not need to be stated.

Response: Thank you for your careful reading. We removed the sentence stating the rationale for the sites chosen from the Settings section.

What will the composition of the fluids used for resuscitation be? Crystalloid? Colloid? Blood products? If the composition of the fluids is left to the discretion of the treating physician in both arms of the study this should be stated. Or if they are controlled please elaborate on this.

Response: Thank you for allowing us to develop this point.

In Methods/Design (Study interventions) we added:

”The ICU physician may recommend fluid therapy or vasoactive drugs with types and amounts at his/her choice. However, when signs of moderate/severe pulmonary congestion are seen on LUS exam (BLS ≥15), a negative 24-hour fluid balance (250-1000 ml) will be intended according to clinical judgement.”

Sample size calculation:

Last sentence starting "In our opinion…” is not needed.

Response: We removed this last sentence from the Sample size calculation section.

Strengths and Limitations of study

Given the risk of protocol non-compliance will you analyze the data on an intention to treat basis?

Response: Main data will be analyzed on an intention to treat basis.

In Statistical analysis section we wrote:

”Statistical analysis will be performed using SPSS (SPSS Inc., Chicago, IL, USA) and conducted on an intention-to-treat basis.”
* I agree with the investigators that this RCT cannot be blinded. Did they take any measures to prevent bias related to an unblinded intervention?

Response: The optimal strategy to minimize bias related to unblinded intervention is to blind all other researchers not involved in delivering the intervention.

In Randomization and blinding section we stated:

” Due to study design, patients and ICU physicians cannot be blinded, but the researcher that investigates primary and secondary outcomes will be blinded to patient group assignment.”

* End Points and Main Outcome Measures. - When is a patient considered to have completed the study? What is the end point for each individual patient?

Response: Thank you for allowing us to clarify these important points.

In the revised version of the manuscript we made the following changes:

In Abstract we wrote:

„The trial intervention will start on ICU admission and will consist in daily assessment of BLS and triggered evacuation of excessive fluids with loop diuretics (Furosemide) when BLS ≥15. If rebalancing volume status with diuretics fails, forced evacuation by ultrafiltration will be used. The main endpoint is death from all causes at 28 days from randomization.”

In Methods/Design (Study Design) we added:

” While hospitalized in ICU, participants will be randomly assigned to receive LUS guided fluid management or usual care, until ICU discharge or for up to 28 days after randomization, whichever comes first.

The main endpoint will be all-cause mortality at 28 days from randomization (ICU admission).”

In Methods/Design (Study interventions) we changed the last words of the first phrase, ”during ICU stay”, with ” until ICU discharge, or for up to 28 days after randomization, whichever comes first” The phrase is read now:

” LUS guided fluid management is based on BLS assessment using LUS, within the first 24 hours of ICU admission, and daily thereafter, until ICU discharge, or for up to 28 days after randomization, whichever comes first.”

In Methods/Design (Primary outcome) we changed ”The main outcome will be 28-day survival.” with ” The main outcome will be death from all causes at 28 days from randomization.”
MINOR ESSENTIAL REVISIONS (not for publication)

Study Interventions: You do not state what time of day the follow up LUS will be performed. Will they be performed at set times, or at set intervals from the first ultrasound?

Response: Thank you for raising this important point. We have provided more details regarding the time of day the follow-up LUS exams will be performed.

In Methods/Design (Study interventions) we added:

“After the initial LUS examination, the follow-up LUS will be performed daily, in the morning, at set times, between 9 and 11 am. The rationale for this approach is that all ICU patients will have daily, in the morning a full clinical examination and a complete set of laboratory tests, providing evaluation of fluid status. In this way, all collected data may be further correlated with LUS findings.”

Keywords. - Three to 10 key words chosen according to the list of Medical Subject Headings (MeSH) provided by the Index Medicus must be added. Please, add, "randomized controlled trial".

Response: Thank you for your suggestion. We added "randomized controlled trial" to the Keywords.

References.

The references must be formatted according to the editorial standards of the journal TRIALS.

* In the body text, references must be reported with plain text and between brackets; thus, they must look like [1-3] rather than [1] [2].

* The list of authors must be ended by a colon ( : ) rather than a period ( . ) (all references).

* The title must be printed in bold characters.

* The name of the journal must be in italics (all references).

* No dot at the end of a journal name (all references).

* Put a comma after year of publication (example: 1999, 200:149-170).

* Volume must be printed in bold characters.

* Delete number of issue (many references).
Response: We apologize for the errors found in References section.

We have made the suggested corrections. We also modified the way in which references are reported in the body text, as you suggested.

CONCLUSION.

I worry that assessing the fluid status of ICU patients once a day will not be sufficient to categorize and evaluate patients sufficiently given that fluid resuscitation and volume status can rapidly change over 24 hours in the ICU. A patient found to be fluid neutral by ultrasound can quickly progress to fluid overload prior to the next ultrasound. Conversely, a patient started on diuretic therapy could be quickly progress to intravascular depletion if they have a robust response to diuretics.

* The study is relevant: objective assessment of fluid status in ICU patients is needed and of utmost importance.

* The research question is clear: can LUS improve outcomes by monitoring fluid status in the ICU.

* The design of the study has flaws as enumerated above and acknowledged by the authors themselves. The heterogeneity of the patient population enrolled may make detecting a difference between the two groups difficult as will individual physician non-compliance with the protocol.

I believe that this manuscript is almost ready to be published. It can be considered for publication if the editors of the journal Trial considers that this paper is of interest for his readership.

Response: Thank you for the appreciations and for the encouraging comments.

We recognize that a hemodynamically unstable patient will require more than one evaluation of fluid status during the day. However, we believe that even one LUS examination per day can add valuable informations in the decision making process of what fluid strategy should be adopted in an ICU patient. By allowing an early detection of overhydration, LUS may help physicians to refine fluid management in ICU patients, and to avoid whenever possible, an unnecessary positive cumulative fluid balance. In this way, at the end of the ICU stay, the patients will have a better fluid status which may improve their outcome.

Jesse Wenger (Reviewer 3)
Rusu et.al. propose to perform a clinical trial where critically ill patients are randomized to a fluid management strategy where patients either receive standard ICU care for fluid management or lung ultrasound guided fluid management with the administration of diuretics. Rusu et. al. nicely state that fluid overload or inappropriately given fluids are associated with worse patient outcomes. They also highlight that lung ultrasound provides a fast easy and reliable way to assess extravascular lung water. Point of care ultrasound is frequently used in the ICU by clinicians to help direct patient care but more clinical data is needed to help clinicians determine how best to apply this technology to the critically ill patient. Since it is often a struggle to assess fluid balance in the ICU, I think the essential question of this study protocol- can I improve assessment and management of fluid overload with lung ultrasound- to be an important one. However, I have a few reservations with the protocol as written.

Response: Thank you. We highly appreciate your review of our manuscript.

1) I am concerned that with the control group, this study will not effectively test whether lung ultrasound can help with fluid balance and improve patient outcomes, but rather the study will assess if a group where there is an elevated awareness of fluid overload with a diuretic protocol will do better than a group where there is less awareness of fluid overload and no diuretic protocol. It would seem that in addition to daily fluid balance, other measurements of fluid overload (chest xray, weight) would be helpful to assess in both groups and understand how each group compares with usual measurements of fluid overload. Perhaps both groups should have lung ultrasound performed and BLS assessed but only one group be given diuretics dictated by BLS?

Response: Thank you for sharing your thoughts and concerns on our study protocol.

Fluid therapy is a cornerstone of ICU treatment and an objective assessment of fluid status in ICU patients is of utmost importance. However, this may be challenging in the ICU settings, as standard measurements to detect fluid overload are known to be of limited value, and the use of other more precise measurements is variable.

The results of all fluid assessment methods will be collected in studied patients.

Point of care ultrasound is already part of the critical care patient management. However, there are still doubts whether LUS is reliable in assessing fluid status in ICU patients. In our trial, in the active group, fluid overload is defined based on LUS findings (BLS ≥15) and the algorhythm of fluid depletion is based on BLS. It is possible that many patients in the active group will benefit of a more judicious fluid administration based on daily BLS assessment.

2) Since the intervention group will potentially be more likely to receive RRT, there is the potential for more complications in this group. I did not read in the protocol a way to track or account for these potential complications (increased risk of infection, more hypotension, need for transfusion, etc).
Response: All complications related to the RRT use will be accounted.

In Data collection and follow-up section we stated:

“Presence and time-course evolution of organ dysfunctions, as well as specific therapeutic interventions will be recorded accordingly: hemodynamic support (drug type, dose and duration of treatment), respiratory support (number of hours on mechanical ventilation), RRT (type, duration, dose of dialysis, volume of removed fluid, pre and post dialysis BLS in active group only).”

In the revised version of the manuscript we added:

“All complications related to the RRT use will be recorded.”

3) Would you allow the addition of low dose pressors to achieve fluid goals in the intervention group? I was not able to tell from the current protocol.

Response: Thank you for giving us the opportunity to clarify this aspect.

In Methods/Design (Study interventions) we added:

” The ICU physician may recommend fluid therapy or vasoactive drugs with types and amounts at his/her choice. However, when signs of moderate/severe pulmonary congestion are seen on LUS exam (BLS ≥15), a negative 24-hour fluid balance (250-1000 ml) will be intended according to clinical judgement.”

4) It may be helpful to have a "quality" check or inter-rater reliability on lung ultrasound scoring with scans being read by another provider to verify the lung ultrasound score.

These concerns will likely need to be explored in the final manuscript after the data is collected and analyzed.

Response: Thank you for your thoughtful comment.

All investigators involved in performing LUS were previously assessed for the ability to perform LUS, to identify B-lines, and to determine BLS. The inter-rater reliability was evaluated by analysing the scores of the examiners using intraclass correlation coefficient. All concerns related to inter-observer reliability will be explored when reporting trial data results.