The authors should be applauded for conducting a trial utilizing ketamine for RSE. The vast amount of literature on this drug's application in SE/RSE is extremely interesting and hopeful. I've been following the vast majority of publications in this area for some time now. This trial will be a major step forward into gaining wider acceptance of its application in this context.

Overall, the proposal as written is sufficient for publication. I've included some minor suggestions below (either for this manuscript or to consider during the data collection and analysis post-trial).

1. Duration of ketamine trial until "failure" is determined?
2. How/who determines the duration of "successful" therapy (ie 48hr to 7 days)?
3. Specific criteria for "adverse effects" leading to discontinuation of therapy. Specifically for the ketamine groups and propofol groups. For example: propofol - intensivist dependent decision "the urine is a little green, I'm stopping", etc... Would be nice to have defined criteria to stopping the drug in the setting of "adverse events" (specific hemodynamic, laboratory criteria, etc.)
4. Who is interpreting the EEG in order to determine "success" vs. "failure"? Are they blinded to the treatment? Something to consider.
5. The secondary outcomes are excellent. Might consider looking at VAP/HAP rates (almost certainly will be higher in the control arm), sepsis, decubitus ulcers, DVT/PE, trach status, etc...
6. Also documenting the adverse events secondary to vasopressor...

Additional Comments:
- Consideration of alternative therapies for RSE, especially in children.
- Importance of standardizing treatment protocols across centers.
- Further research on long-term outcomes and follow-up data.
utilization.

The above are just for consideration. I look forward to the results of this study.

| REVIEWER | Elisa Ballardini  
Department of Medical Sciences  
Pediatric Section  
Neonatal Intensive Care Unit  
University Hospital S.Anna Ferrara, Italy. |
| REVIEW RETURNED | 10-Mar-2016 |

| GENERAL COMMENTS | Congratulations on the study protocol. I believe it is well designed, clear and could be really relevant to improve clinical practice. I bring to your attention only two doubts. I would be concerned about a possible bias due to the heterogeneous aetiology of RCSE and, also for this reason, of a premature interruption of the study using the sequential model. Probably, the presence in your team of two experts in statistics will avoid this bias during the enrollment process. Thank you for the opportunity to review your study protocol. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer 1
1. Duration of ketamine trial until "failure" is determined?
   **ANSWER:** The duration of the ketamine trial until failure is recorded but a stratified analysis by treatment duration is not planned.

2. How/who determines the duration of "successful" therapy (ie 48 hr to 7 days)?
   **ANSWER:** The duration of "successful" therapy is assessed by the neurologist using EEG recordings (see section “The experimental arm: KE”, page 9).

3. Specific criteria for "adverse effects" leading to discontinuation of therapy. Specifically for the ketamine groups and propofol groups. For example: propofol - intensivist dependent decision "the urine is a little green, I'm stopping", etc... Would be nice to have defined criteria to stopping the drug in the setting of "adverse events" (specific hemodynamic, laboratory criteria, etc.)
   **ANSWER:** The stopping rules for toxicity are defined according to the Common Toxicity Criteria for Adverse Events (CTCAE). Considering the safety profile of the study drugs and their most frequent adverse events, the occurrence of grade 4 cardiac events (hypotension possibly related to propofol, hypertension and tachycardia possibly related to ketamine) leads to the discontinuation of therapy. In any case, the investigator will discontinue study treatment for patients who develop unacceptable toxicity (i.e. toxicity that does not recover or cannot be tolerated or medically controlled). The reference regarding the CTCAE has been added to the bibliography.

4. Who is interpreting the EEG in order to determine "success" vs. "failure"? Are they blinded to the treatment? Something to consider.
   **ANSWER:** The neurologist interprets the EEG and determines the “success” or “failure” of the treatment, which is not blinded. The lack of blindness is required to avoid unnecessary endotracheal intubation for those patients treated with KE.

5. The secondary outcomes are excellent. Might consider looking at VAP/HAP rates (almost certainly will be higher in the control arm), sepsis, decubitus ulcers, DVT/PE, trach status, etc... Also
documenting the adverse events secondary to vasopressor utilization.

ANSWER: The study does not have the power to detect VAP/HAP, decubitus ulcer, etc. The estimated sample size is 57 patients and the events rate is lower than 1%. Following the reviewer’s suggestion, all these events will be taken into account.

Reviewer 2
1. I would be concerned about a possible bias due to the heterogeneous aetiology of RCSE and, also for this reason, of a premature interruption of the study using the sequential model.

ANSWER: The randomization is stratified by age, which is related to aetiology in the paediatric population. However, due to the rarity of refractory convulsive status epilepticus and the heterogeneous nature of the aetiology, an analysis stratified by aetiology is not possible.

VERSION 2 – REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Frederick A. Zeiler</th>
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<tbody>
<tr>
<td>University of Manitoba</td>
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<tr>
<td>REVIEW RETURNED</td>
<td>05-Apr-2016</td>
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</tbody>
</table>

| GENERAL COMMENTS          | The authors have addressed my previous concerns. The article is ready for publication. |
Efficacy of ketamine in refractory convulsive status epilepticus in children: a protocol for a sequential design, multicentre, randomised, controlled, open-label, non-profit trial (KETASER01)

Anna Rosati, Lucrezia Ilvento, Manuela L’Erario, Salvatore De Masi, Annibale Biggeri, Giancarlo Fabbro, Roberto Bianchi, Francesca Stoppa, Lucia Fusco, Silvia Pulitano, Domenica Battaglia, Andrea Pettenazzo, Stefano Sartori, Paolo Biban, Elena Fontana, Elisabetta Cesaroni, Donatella Mora, Paola Costa, Rosanna Meleleo, Roberta Vittorini, Alessandra Conio, Andrea Wolfler, Massimo Mastrangelo, Maria Cristina Mondardini, Emilio Franzoni, Kathleen S McGreevy, Lorena Di Simone, Alessandra Pugi, Lorenzo Mirabile, Federico Vigevano and Renzo Guerrini

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