Author’s response to reviews

Title: Continuous wound infusion of local anesthetic and steroid after major abdominal surgery: study protocol for a randomized controlled trial

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Version: 4 Date: 23 June 2015

Author’s response to reviews: see over
Dear Editor in Chief;

We would like to thank You and the Reviewer for considering our article for publication in 
Trials. Thanks for Your precious suggestions, that will give us the opportunity to improve the 
quality of our work.

We have read all the comments, and modified the text as suggested.

Please, find below a point-by-point answer to comments. We enclose the paper with 
highlighted modifications.

Editorial requests:

1. Please ensure the title conforms to journal style for study protocol articles. The title 
should follow the format ?_________: study protocol for a randomized controlled trial.? 
Please note that the title in the submission system should match that of your manuscript. 
We did it.

2. Please indicate the corresponding author on the title page. We did it.

3. Please include the trial registration number at the end of the Abstract, along with the 
date of registration. We included it.

4. Please rename the Rationale, 'Background'. We did it.

5. Please include the full names of all ethical bodies that approved your study in the 
various centres involved, along with the reference numbers if possible. If you do not wish 
to list them all in the Methods section, please include the list as an additional file and refer 
to this in the Methods section. We included all the ethical bodies.

6. Please replace the Conclusions section with a Discussion section. We did it.

7. Please include a Competing Interests section after the list of abbreviations. If the 
authors have no competing interests, please state: "The authors declare that they have no 
competing interests." We did it.

8. Please mention each author individually in your Authors' Contributions section. We 
suggest the following kind of format (please use initials to refer to each author's 
contribution): ?AB carried out the molecular genetic studies, participated in the sequence 
alignment and drafted the manuscript. JY carried out the immunoassays. MT participated 
in the sequence alignment. ES participated in the design of the study and performed the 
statistical analysis. FG conceived of the study, and participated in its design and 
coordination and helped to draft the manuscript. All authors read and approved the final 
manuscript.? Please ensure that you explain that all authors have read and approved the
Reviewer’s report

Title: Continuous wound infusion of local anesthetic and steroid after major abdominal open surgery: a multicenter, double blind, phase III clinical trial  Version: 3  Date: 26 May 2015

Reviewer: Jo Dumville

Reviewer’s report:

1. The author should follow the headings used in protocols published in Trials Journal for example Background rather than Rationale etc. Could the authors go through and restructure as required. We restructured the manuscript according to your suggestion.

2. All abbreviations need to be defined at first use – for example – CWI in the background. It is defined in the abstract but I think needs to be defined again in first use in the main text. We did it.

3. Overall I think that the number of abbreviated terms could be reduced – there are quite a lot – I would suggest only abbreviating 2 or 3 key terms and having the rest of terms written in full throughout. We reduced the abbreviations according to your suggestions. They are more than 3, but halved comparing to the manuscript’s previous version; we maintained only the abbreviations for the terms and genes that are extensively used in the text.

4. The background is relatively clear although it does need proof reading and copy edit will be required to enhance readability so that the flow and meaning of the text is crisp and clear. There are issues with switching between past and present tense in some places throughout text. We edited the text.

5. I think that the background could be improved by the additional of one or two sentences at the end to link the background material to the proposed trial. For example there is discussion of how individual’s genetics might impact on pain. This suggests that there will be a genetic element to the trial but this is not apparent at the background stage – nor from the study title. I think the relevance of this material to the proposed study needs to be highlighted. The aims of the study currently appear mid-way through the paper – essentially they need to be moved upwards. We added some sentences at the end of background to highlight the aims of the study and genetic investigations.

6. When discussing inclusion criteria can the authors be more specific about what is defined as major abdominal surgery? We better specified the type of surgeries that are considered for the inclusion in the study.

7. The discussion of how randomisation occurs needs to be moved up I think to when randomisation is first mentioned. The authors state that they will use opaque, sealed envelopes: could they clarify that these will also be sequentially numbered. Whilst they
discuss how the allocation will occur. I don’t think there is any discussion of how the randomisation sequence is actually generated. Random group allocation of patients is made through a computer-generated sequence. Envelopes are sequentially numbered. We better explained in the text.

8. I think that information about the outcomes should be presented separately from the aims. I also think that the wording around the outcomes needs to be reconsidered. I would not use the word verify. I also think that the wording needs to be clearer – so the primary outcome as I understand it is amount of rescue analgesics required – is this correct? I think this needs to be stated more clearly. We rephrased and re-organized the outcome section (separated from aims) according to your indication; the primary outcome is morphine equivalents consumption over 7 days, and we did eliminate the word “verify”.

9. The author then talk about primary endpoints and secondary end points. I was not clear what the difference between outcomes and endpoints were. This needs to be made clearer. It was also not clear to me what measures were being used to assess ‘pain values’ and other elements of pain. We separated primary and secondary endpoints. Pain is assessed with NRS scale (at rest and movement – i.e. coughing and deep inspiration – 11 point scale from 0 = no pain and 10 = worst imaginable pain) and other analgesics’ consumption (meaning additional paracetamol / tramadol + the total amount of bolus required via Patient Controlled Intrawound Analgesia).

10. Also related to secondary outcomes/endpoints – the authors state that they will measure side effects. I think more detail is required. Earlier on in the text monitoring of wound healing and infection are mentioned – are these related to outcomes/side effects. In general I think all the information about outcomes needs to be put in one place with a clear specification of what outcomes are and how and when they are measured. We specified more about outcomes and side effects.

11. The sample size calculation needs more detail – if possible any further detail about how the difference was decided on would be useful. The authors note clinical experience – was this recorded in some way – e.g. via an audit of use of pain meds. Is there any data from other studies that support this difference of 50% (which is large and leads to a small sample size). Further justification would be useful. The attrition rate used in the calculation would also be useful. We added further justifications, as you required. Our hypothesis comes from 1) our retrospective experience and audits about analgesic consumption in our Institution and 2) data from previous literature; they both showed reduction in morphine consumption of 30-50% in patients treated with local anesthetic wound infusion. We aim for a high clinically meaningful reduction of 50% in all patients, since we are adding methylprednisolone in wound infusion and we wish to gain the maximum analgesic efficacy. Attrition rate 15-20%.

12. The discussion of drop-outs is brief and unclear. The authors note that they consider anyone not complete the treatment as a drop-out. It would be reassuring if the authors can confirm that they will be conducting an intention to treat analysis and that all participants will be analysis where possible. Any approaches that will be taken to deal with missing data could usefully be discussed here. Sorry, that part was unclear. Actually, we are performing an ITT, since we considered all patients once enrolled in the study. Drop-out are patients not completing evaluation at 3 months (for any reason), but we keep evaluating all patients, once enrolled, even if they remove the catheter before the 7th day and they do not receive the protocol’s treatment. We corrected, as you required.
13. The analysis section is very brief. I think more detail about the analyses planned for the primary outcome and then each secondary outcome would be clearer. Again I think that the detail around the use of repeated measures is too limited. At this stage the protocol should be able to contain the same level of analytical detail as the final paper would. *We revised the analysis section, being more specific.*

14. At the end of the protocol I remained unclear about how the genetic data, the IR data and the Oxidative stress data was going to be used. The aims suggest that they will be assessed to see if they are biological markers that help modulate post-operative and persistent pain. I think the analysis section could pre-specify the analysis that will be done as part of this exploration. *We revised the analysis section, being more specific.*

On behalf of all the authors

Kind regards

Dr. Dario Bugada